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PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

Abstract:

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Agonist antibodies are disclosed which bind to the extracellular domain of receptor protein tyrosine kinases pTKs, and thereby cause dimerization and activation of the intracellular tyrosine kinase domain thereof. The antibodies are useful for activating their respective receptor and thereby enabling the role of the tyrosine kinase receptor in cell growth and/or differentiation to be studied. Chimeric proteins comprising the extracellular domain of the receptor pTKs and an immunoglobulin constant domain sequence are also disclosed. Data supplied from the esp@cenet database - Worldwide

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Agonist antibodies are disclosed which bind to the extracellular domain of receptor protein tyrosine kinases pTKs, and thereby cause dimerization and activation of the intracellular tyrosine kinase domain thereof. The antibodies are useful for activating their respective receptor and thereby enabling the role of the tyrosine kinase receptor in cell growth and/or differentiation to be studied. Chimeric proteins comprising the extracellular domain of the receptor pTKs and an immunoglobulin constant domain sequence are also disclosed.

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PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel protein tyrosine kinase (pTK) genes, the proteins encoded by these genes, RNA nucleic acid sequences which hybridize to the genes, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use therefor.

In particular, this application relates to agonist antibodies which are able to activate the tyrosine kinase domain of the receptor pTKs disclosed herein and pTK-immunoglobulin chimeras.

DESCRIPTION OF RELATED ART

Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases are enzymes that catalyze this process. Moreover, many act as growth factor receptors. The c-kit subgroup of receptor tyrosine kinases catalyze the phosphorylation of exogenous substrates, as well as tyrosine residues within their own polypeptide chains (Ullrich *et al.*, Cell 61:203 [1990]). Members of the c-kit subgroup include FLT/FLK (Fetal Liver Kinase), FGF (Fibroblast Growth Factor Receptor) and NGF (Nerve Growth Factor Receptor).

The *EPH* tyrosine kinase subfamily, Eph, Elk, Eck, Eek, Hek, Hek2, Sek, Ehk-1, Ehk-2, Cek-4 to -10, Tyro 1, 4, 5 and 6, appears to be the largest subfamily of transmembrane tyrosine kinases (Hirai *et al.*, Science 238:1717-1720 [1987]; Letwin *et al.*, Oncogene 3:621-678 [1988]; Lhotak *et al.*, Mol. Cell. Biol. 13:7071-7079 [1993]; Lindberg *et al.*, Mol. Cell. Biol. 10:6316-6324 [1990]; Bohme *et al.*, Oncogene 8:2857-2862 [1993]; and Wicks *et al.*, Proc. Natl. Acad. Sci. USA. 89:1611-1615 [1992]; Pasquale *et al.* Cell Regulation 2:523-534 [1991]; Sajjadi *et al.*, New Biol. 3:769-778 [1991]; Wicks *et al.*, Proc. Natl. Acad. Sci. USA. 89:1611-1615 [1992]; Lhotak *et al.*, Mol. Cell. Bio. 11:2496-2502 [1991]; Gilardi-Hebenstreit *et al.*, Oncogene 7:2499-2506 [1992]; Lai *et al.*, Neuron 6:691-704 [1991]; Sajjadi *et al.*, Oncogene 8:1807-1813 [1993]; and Maisonpierre *et al.*, Oncogene 8:3277-3288 [1993]).

Additional pTKs and agonist antibodies thereto are needed in order to further study growth and differentiation of cells, for use as therapeutic agents and for diagnostic purposes. Accordingly, it is an

object of the present invention to provide novel pTK genes, the proteins encoded thereby, antibodies specific for the encoded proteins, chimeras of the proteins and methods of use thereof.

SUMMARY OF THE INVENTION

The genes isolated as described herein are referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes". The nucleic acid sequences of some of these genes, isolated as discussed herein, show significant homology with previously identified protein tyrosine kinases containing extracellular domains, which function as growth factor receptors (*e.g.*, pTKs of the c-kit subgroup). Some of the pTK genes have been shown to be present in both megakaryocytic and lymphocytic cells.

In particular, fourteen pTK genes have been identified. Two pTK genes, referred to as SAL-S1 and SAL-D4 were identified in megakaryocytic cells. SAL-D4 is related to the CSK family of intracellular pTKs and SAL-S1 is related to the FGF receptor family of pTKs. Five pTK genes, referred to as LpTKs, were identified in lymphocytic cells and have been shown to be present in megakaryocytes as well. One pTK gene, referred to as HpTK5, was identified in human hepatoma cells. Six pTK genes, referred to as bpTK genes, were found in human brain tissue.

The pTK genes, which are the subject of the present invention, were generally identified using two sets of degenerative oligonucleotide primers: a first set which amplifies all pTK DNA segments (SEQ ID NOS: 1-2), and a second set which amplifies highly conserved sequences present in the catalytic domain of the c-kit subgroup of pTKs (SEQ ID NOS: 3-4). The pTK genes identified in this manner are described below.

SAL-S1 is expressed in several megakaryocytic cell lines, but not in erythroid cell lines. The nucleotide sequence of part of SAL-S1 was obtained, revealing a sequence containing 160 base pairs (SEQ ID NO: 5). This isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 6) which exhibited significant sequence homology with known protein tyrosine kinases of the FLT/FLK family. The deduced amino acid sequence of SAL-S1 (SEQ ID NO: 32) contains 1298 residues.

SAL-D4, also expressed in megakaryocytic cells, is a DNA fragment containing the nucleotide sequence of 147 base pairs. (SEQ ID NO: 7). This isolated DNA fragment encoded an amino acid sequence (SEQ ID NO: 8) which exhibited significant sequence homology with known protein tyrosine kinases of the CSK intracellular pTK family.

The LpTKs, including LpTK 2, LpTK 3, LpTK 4, LpTK 13 and LpTK 25, are expressed in lymphocytic cells, as well as megakaryocytic cells. The nucleotide sequence (151 base pairs) of the LpTK 3 gene was obtained (SEQ ID NO: 11). The nucleotide sequences of the LpTK 2, LpTK 4, and LpTK 13 genes contained 149 base pairs (SEQ ID NO: 9), 137 base pairs (SEQ ID NO: 13), and 211 base pairs (SEQ ID NO: 15) respectively. LpTK 25 has a nucleotide sequence of 3120 b.p. (SEQ ID NO: 22). A full length gene sequence has been obtained for LpTK 2 (SEQ ID NO: 19) which contains 7607 b.p. Additional sequencing of LpTK 4 revealed a sequence of 404 b.p. (SEQ ID NO: 21).

The HpTK5 gene, expressed in human hepatoma cells, has a nucleotide sequence of 3969 b.p. (SEQ ID NO: 23).

Nucleotide sequences of the bpTKs, including bpTK 1, bpTK 2, bpTK 3, bpTK 4, bpTK 5 and bpTK 7, are expressed in human brain tissue and encode proteins having the amino acid sequences of SEQ ID NOS: 25-29 and 34 respectively.

Thus, the present invention includes DNA isolated from a human megakaryocytic cell line, which hybridizes to DNA encoding an amino acid sequence which is highly conserved in the catalytic domain of protein tyrosine kinases of the c-kit subgroup.

The present invention also includes the proteins encoded by the pTK genes identified as described herein, which exhibit significant sequence homology with members of the c-kit subgroup of pTKs as well as the proteins encoded by HpTK5 and the bpTKs. The present invention also includes SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK homologues or equivalents (*i.e.*, proteins which have amino acid sequences substantially similar, but not identical, to that of SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which exhibit tyrosine kinase activity). This invention further includes peptides (SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK fragments) which retain tyrosine kinase activity, yet are less than the entire SAL-S1, SAL-D4, LpTK, HpTK5 and bpTK sequences; and uses for the SAL-S1, SAL-D4, the LpTK, HpTK and the bpTK nucleic acid sequences and SAL-S1, SAL-D4, LpTK, HpTK and bpTK equivalents.

The present invention further includes nucleic acid sequences which hybridize with DNA or RNA encoding the proteins described herein, which exhibit significant sequence homology with the FLT/FLK, FGF receptor or NGF receptor family of protein tyrosine kinases contained within the c-kit subgroup. Such nucleic acid sequences are useful as probes to identify pTK genes in other vertebrates, particularly mammals, and in other cell types.

They can also be used as anti-sense oligonucleotides to inhibit protein tyrosine kinase activity, both *in vitro* and *in vivo*.

The SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases of the present invention can be used as target proteins in conjunction with the development of drugs and therapeutics to modulate cell growth, differentiation and other metabolic functions. The SAL-S1, SAL-D4, LpTK, HpTK or bpTK proteins can be used as agonists or antagonists to other tyrosine kinases. The pTKs can also be instrumental in the modulation of megakaryocyte and/or platelet adhesion interactions.

In addition, the SAL-S1, SAL-D4, LpTK, HpTK and bpTK tyrosine kinases can be used in screening assays to detect cellular growth and/or differentiation factors. Using standard laboratory techniques, the ligands of the pTKs of the present invention can be identified. In particular, the invention provides chimeric pTK-immunoglobulin fusion proteins which are useful for isolating ligands to the pTKs disclosed herein. The chimeric proteins are also useful for diagnostic assays designed to detect these ligands present endogenously, within cells, as well as exogenously, in extra-cellular fluids. Assays, using the chimeric proteins, can also be designed as diagnostic aids to detect these ligands in body fluids such as blood and urine.

In another aspect, the invention provides antibodies specific for SAL-S1, SAL-D4, the LpTKs, HpTK5 and the bpTKs, which are optionally agonists for their respective pTK (where the pTK is a receptor). The invention also concerns a hybridoma cell line and an isolated nucleic acid encoding a monoclonal antibody as herein defined.

Also, the invention pertains to a method for activating a pTK as herein disclosed, comprising reacting the pTK with an agonist antibody thereto. In a different aspect, the invention concerns a method for enhancing cell growth and/or differentiation comprising administering to a human patient in need of such treatment a physiologically effective amount of an agonist antibody which activates a pTK as herein disclosed.

In a still further aspect, the invention concerns a method for detecting a pTK by contacting a source suspected of containing the pTK with a detectably labeled monoclonal antibody which reacts immunologically with the pTK, and determining whether the antibody binds to the source.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict the nucleotide sequence of SAL-S1 (SEQ ID NO: 5) and its deduced amino acid sequence (SEQ ID NO: 6).

Figures 2A and 2B depict the nucleotide sequence of SAL-D4 (SEQ ID NO: 7) and its deduced amino acid sequence (SEQ ID NO: 8).

Figure 3A depicts the nucleotide sequence of LpTK 2 (SEQ ID NO: 9) and its deduced amino acid sequence (SEQ ID NO: 10).

Figure 3B depicts the nucleotide sequence of LpTK 3 (SEQ ID NO: 11) and its deduced amino acid sequence (SEQ ID NO: 12).

Figure 3C depicts the nucleotide sequence of LpTK 4 (SEQ ID NO: 13) and its deduced amino acid sequence (SEQ ID NO: 14).

Figure 3D depicts the nucleotide sequence of LpTK 13 (SEQ ID NO: 15) and its deduced amino acid sequence (SEQ ID NO: 16).

Figures 4A-4I depict the nucleotide sequence (SEQ ID NO: 17) of SAL-S1 and its deduced amino acid sequence (SEQ ID NO: 18).

Figures 5A-5K depict the full length nucleotide sequence (SEQ ID NO: 19) of LpTK2 and its deduced amino acid sequence (SEQ ID NO: 20).

Figure 6 depicts the partial nucleotide sequence (SEQ ID NO: 21) for LpTK4.

Figures 7A-7C depict the full length nucleotide sequence (SEQ ID NO: 22) for LpTK25.

Figures 8A-8I depict the full length nucleotide sequence (SEQ ID NO: 23) and the deduced amino acid sequence of HpTK5 (SEQ ID NO: 24).

Figure 9 depicts the amino acid sequence (SEQ ID NO: 25) of bpTK1.

Figure 10 depicts the amino acid sequence (SEQ ID NO: 26) of bpTK2.

Figure 11 depicts the amino acid sequence (SEQ ID NO: 27) of bpTK3.

Figure 12 depicts the amino acid sequence (SEQ ID NO: 28) of bpTK4.

Figure 13 depicts the amino acid sequence (SEQ ID NO: 29) of bpTK5.

Figure 14 depicts the amino acid sequence (SEQ ID NO: 30) of bpTK7.

Figures 15A-15F depict the full-length nucleotide sequence of SAL-S1 (SEQ ID NO: 31) and its deduced amino acid sequence (SEQ ID NO: 32).

Figures 16A-16H depict the full-length nucleotide sequence of bpTK7 (SEQ ID NO: 33) and its deduced amino acid sequence (SEQ ID NO: 34).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Novel protein tyrosine kinase genes have been identified, their nucleic acid sequences determined, and the amino acid sequences of the encoded proteins deduced. The genes isolated as described herein are

referred to, collectively, as "protein tyrosine kinase genes" or "pTK genes".

To facilitate the isolation and identification of these novel pTKs, two sets of DNA probes were used, as described in Example 1. The first set generally consisted of two degenerative oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2) (Matthews, Cell 65:1143 [1991]; and Wilks, Proc. Natl. Acad. Sci. USA 86:1603 [1989]). These sequences were used as primers in a polymerase chain reaction to amplify tyrosine kinase DNA segments (Mullis, *et al.*, Cold Spring Harbor Symp. Advan. Biol. 51:263 [1986]).

The second set generally consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) designed to amplify the nucleic acid sequence which encodes the highly conserved regions of the catalytic domains of the c-kit family of protein tyrosine kinases. These sequences were used as primers in the polymerase chain reaction (PCR) in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced.

In particular, fourteen pTK genes have been identified. Two pTK genes, referred to as SAL-S1 and SAL-D4, were identified in several megakaryocytic cell lines, including CMK 11-5, DAMI, UT-7 and UT-7 grown in erythropoietin, but not in the erythroid cell lines HEL, PMA stimulated HEL cells, or K562. Five pTK genes, referred to as LpTKs, were identified in lymphocytic, as well as in megakaryocytic cells. One pTK gene, referred to as HpTK5, was identified in human hepatoma cells, and six genes, referred to as bpTKs, were identified in human brain tissue.

SAL-S1 (SEQ ID NOS: 6, 18 and 32) encoded by the nucleic acid sequence of SEQ ID NOS: 5, 17 and 31 exhibits significant homology with the FLT/FLK family of pTKs. SAL-S1 has a signal peptide (*i.e.*, amino acid residues 1 to 24 of Figure 15); extracellular domain (*i.e.*, amino acid residues 25 to 775 of Figure 15); transmembrane domain (*i.e.*, amino acid residues 776 to 800 of Figure 15) and a cytoplasmic tyrosine kinase domain (*i.e.*, amino acid residues 801 to 1298 of Figure 15). SAL-D4 (SEQ ID NO: 8) encoded by SEQ ID NO: 7 is related to the CSK family of intracellular pTKs. The LpTKs, LpTK 2 (SEQ ID NOS: 10 and 20) encoded by SEQ ID NOS: 9 and 19; LpTK 3 (SEQ ID NO: 12) encoded by SEQ ID NO: 11; LpTK4 (SEQ ID NO: 14) encoded by SEQ ID NOS: 13 and 21; LpTK13 (SEQ ID NO: 16) encoded by SEQ

ID NO: 15; and LpTK25 encoded by SEQ ID NO: 22, also exhibit sequence homology with known protein tyrosine kinases.

HpTK5 (SEQ ID NO: 24) encoded by SEQ ID NO: 23 and the bpTKs 1, 2, 3, 4, 5 and 7 (SEQ ID NOS: 25-29 and 34 respectively), similarly exhibit sequence homology with known protein tyrosine kinases. BpTK7 encodes a receptor pTK with a signal peptide (*i.e.*, amino acid residues 1-19 of Figure 16); extracellular domain (*i.e.*, amino acid residues 20-547 of Figure 16); and transmembrane domain (*i.e.*, amino acid residues 548-570 of Figure 16). The remaining sequence comprises the intracellular tyrosine kinase domain.

Thus, as described above, DNA molecules which hybridize with DNA encoding amino acid sequences present in the catalytic domain of a protein tyrosine kinase of the c-kit subgroup of protein kinases have been isolated and sequenced. These isolated DNA sequences, collectively referred to as "pTK genes", (and their deduced amino acid sequences) have been shown to exhibit significant sequence homology with known members of pTK families.

Once isolated, these DNA fragments can be amplified using known standard techniques such as PCR. These amplified fragments can then be cloned into appropriate cloning vectors and their DNA sequences determined.

These DNA sequences can be excised from the cloning vectors, labeled with a radiolabeled nucleotide such as ^{32}P and used to screen appropriate cDNA libraries to obtain the full-length cDNA clone.

The pTK genes as described above have been isolated from the source in which they occur naturally, *e.g.*, megakaryocytic and lymphocytic cells. The present invention is intended to include pTK genes produced using genetic engineering techniques, such as recombinant technology, as well as pTK genes that are synthesized chemically.

The deduced amino acid sequences of the pTK genes include amino acid sequences which encode peptides exhibiting significant homology with the catalytic domain of protein tyrosine kinases of the c-kit subgroup of tyrosine kinases. These proteins, encoded by the pTK genes, can include sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence, resulting in a silent change, that is a change not detected phenotypically. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent substitution.

In addition, the protein structure can be modified by deletions, additions, inversion, insertions or substitutions of one or more amino acid residues in the sequence which do not substantially detract from the desired functional tyrosine kinase properties of the peptide.

Modified pTKs of the present invention, with tyrosine kinase activity, can be made using recombinant DNA techniques, such as excising it from a vector containing a cDNA encoding such a protein, or by synthesizing DNA encoding the desired protein mechanically and/or chemically using known techniques.

An alternate approach to producing the pTKs of the present invention is to use peptide synthesis to make a peptide or polypeptide having the amino acid sequence of such a protein, depending on the length of the pTK desired. The peptides or modified equivalents thereof, can be synthesized directly by standard solid or liquid phase chemistries for peptide synthesis.

Preferably, the pTKs of the present invention will be produced by inserting DNA encoding the proteins into an appropriate vector/host system where it will be expressed. The DNA sequences can be obtained from sources in which they occur naturally, can be chemically synthesized or can be produced using standard recombinant technology.

This invention also pertains to an expression vector comprising a pTK gene of the present invention, encoding for a protein which exhibits receptor tyrosine kinase activity.

The pTK genes of the present invention can be used for a number of diagnostic and therapeutic purposes. For example, the nucleic acid sequences of the pTK genes can be used as probes to identify other protein tyrosine kinases present in other cell types, including eukaryotic and prokaryotic cell types.

The nucleic acid sequences can also be used to design drugs that directly inhibit the kinase activity of protein tyrosine kinases, or to design peptides that bind to the catalytic domain of tyrosine kinases, thus inhibiting their activity. These sequences can also be used to design anti-sense nucleotides that can also inhibit, or destroy, tyrosine kinase activity. Such inhibition of tyrosine kinase activity would be desirable in pathological states where decreased cellular proliferation would be beneficial, such as leukemias or other malignancies.

The nucleic acid sequences can also be used to design drugs, peptides or anti-sense nucleotides as above, but with enhancing, rather than

inhibitory effects, on tyrosine kinases. Such enhanced tyrosine kinase activity would result in increasing the phosphorylation of substrates (exogenous, as well as endogenous tyrosine residues). Enhanced effects would be desirable in states where increased cellular proliferation would be beneficial, such as anemias, bleeding disorders and during surgical procedures.

The pTK genes of the present invention can also be used to obtain soluble fragments of receptor tyrosine kinases, capable of binding their respective ligands. pTK genes encoding soluble tyrosine kinase fragments can be produced using recombinant DNA techniques or synthetically. In either case, the DNA obtained encodes a soluble pTK fragment which lacks a substantial portion of the hydrophobic transmembrane region to permit solubilization of the fragment.

These soluble pTK protein fragments can be introduced exogenously to act as competitors with the endogenous, membrane bound pTK for their respective ligands, thus inhibiting tyrosine kinase activity. Alternately, a modified soluble pTK protein fragment can be introduced which binds the ligand but does not activate kinase activity.

These soluble pTK protein fragments can also be used in binding assays to detect ligands such as growth and differentiation factors. Once these ligands are identified, they may be altered or modified to inhibit or enhance kinase activity. For example, the ligands may be modified or attached to substances that are toxic to the cell, such a ricin, thus destroying the target cell. The substance may be a super-activating substance which, after binding to the pTK, may substantially increase the kinase activity, or activate other growth factors.

pTK genes of the present invention would also be useful to develop diagnostic tools for *in vitro* screening assays for ligands such as growth factors or differentiation factors that inhibit or enhance kinase activity. The proteins encoded by the pTK genes can also be used in such assays, or as immunogens to produce monoclonal or polyclonal antibodies to be used in such assays.

In one embodiment of the invention, a chimera comprising a fusion of the extracellular domain of the pTK (where the pTK is a receptor) and an immunoglobulin constant domain can be constructed which can be used to assay for ligands for the receptor and can be used for the production of antibodies against the extracellular domain of the receptor.

The expression "extracellular domain" or "ECD" when used herein refers to any polypeptide sequence that shares a ligand binding function of the extracellular domain of the naturally occurring receptor pTKs disclosed herein. Ligand binding function of the extracellular domain refers to the ability of the polypeptide to bind at least one pTK ligand. Accordingly, it is not necessary to include the entire extracellular domain since smaller segments are commonly found to be adequate for ligand binding. The truncated extracellular domain is generally soluble. The term ECD encompasses polypeptide sequences in which the hydrophobic transmembrane sequence (and, optionally, 1-20 amino acids C-terminal and/or N-terminal to the transmembrane domain) of the mature pTK has been deleted. Thus, the soluble extracellular domain-containing polypeptide can comprise the extracellular domain and the cytoplasmic domain of the pTK. Alternatively, in the preferred embodiment, the polypeptide comprises only the extracellular domain of the pTK. The extracellular and transmembrane domains of the pTK can be readily determined by the skilled practitioner by aligning the pTK of interest with known pTK amino acid sequences for which these domains have been delineated. Alternatively, the hydrophobic transmembrane domain can be readily delineated based on a hydrophobicity plot of the sequence. The extracellular domain is N-terminal to the transmembrane domain.

The term "immunoglobulin" generally refers to polypeptides comprising a light or heavy chain usually both disulfide bonded in the native "Y" configuration, although other linkage between them, including tetramers or aggregates thereof, is within the scope hereof.

Immunoglobulins (Ig) and certain variants thereof are known and many have been prepared in recombinant cell culture. For example, see U.S. Patent 4,745,055; EP 256,654; Faulkner *et al.*, Nature 298:286 [1982]; EP 120,694; EP 125,023; Morrison, J. Immun. 123:793 [1979]; Köhler *et al.*, Proc. Nat'l. Acad. Sci. USA 77:2197 [1980]; Raso *et al.*, Cancer Res. 41:2073 [1981]; Morrison *et al.*, Ann. Rev. Immunol. 2:239 [1984]; Morrison, Science 229:1202 [1985]; Morrison *et al.*, Proc. Nat'l. Acad. Sci. USA 81:6851 [1984]; EP 255,694; EP 266,663; and WO 88/03559. Reassorted immunoglobulin chains also are known. See for example U.S. patent 4,444,878; WO 88/03565; and EP 68,763 and references cited therein. The immunoglobulin moiety in the chimera of the present invention may be obtained from IgG_1, IgG_2, IgG_3, or IgG_4 subtypes, IgA, IgE, IgD or IgM, but

preferably IgG_1 or IgG_3. Most preferably, the immunoglobulin moiety is the Fc portion of IgG-γ.

The terms "chimera comprising a fusion of an extracellular domain of a pTK with an immunoglobulin constant domain sequence" or "pTK-immunoglobulin chimera" refer to a polypeptide comprising an extracellular domain coding amino acid sequence of a pTK conjugated to an immunoglobulin constant domain sequence. This definition includes chimeras in monomeric, homo- or heteromultimeric, and particularly homo- or heterodimeric, or -tetrameric forms.

A preferred embodiment is the fusion of the C-terminus of the extracellular domain of a pTK, to the N-terminus of the C-terminal portion of an antibody (in particular the Fc domain), containing the effector functions of immunoglobulin G_1. In a preferred embodiment, the entire heavy chain constant region is fused to the extracellular domain. In another preferred embodiment, a sequence beginning in the hinge region just upstream of the papain cleavage site (which defines IgG Fc chemically; residue 216, taking the first residue of heavy chain constant region to be 114 (Kabat *et al.*, Sequences of Immunological Interest, National Institutes of Health, Bethesda, MD, [1987]), or analogous sites of other immunoglobulins) is fused to the ECD of the pTK.

In a particularly preferred embodiment, the pTK extracellular domain is fused to the hinge region and C_H2 and C_H3 or C_H1, hinge, C_H2 and C_H3 domains of an IgG_1, IgG_2 or IgG_3 heavy chain. The precise site at which the fusion is made is not critical, and the optimal site can be determined by routine experimentation. A principal advantage of the chimeras is that they are secreted into the culture medium of recombinant hosts, although the degree of secretion might be different for various expression systems.

In general, the chimeras of the present invention are constructed in a fashion similar to chimeric antibodies in which a variable domain from an antibody of one species is substituted for the variable domain of another species. See, for example, EP 0 125 023; EP 173,494; Munro, Nature 312: [13 December 1984]; Neuberger *et al.*, Nature 312: [13 December 1984]; Sharon *et al.*, Nature 309: [24 May 1984]; Morrison *et al.*, Proc. Nat'l. Acad. Sci. USA 81:6851-6855 [1984]; Morrison *et al.* Science 229:1202-1207 [1985]; Boulianne *et al.*, Nature 312:643-646 [13 December 1984]; Capon *et al.*, Nature 337, 525-531 [1989]; Traunecker *et al.*, Nature 339, 68-70 [1989].

To prepare the pTK-Ig chimeric polypeptides, the DNA including a region encoding the desired pTK sequence is cleaved by a restriction enzyme at or proximal to the 3' end of the DNA encoding the immunoglobulin-like domain(s) and at a point at or near the DNA encoding the N-terminal end of the mature pTK (where use of a different leader is contemplated) or at or proximal to the N-terminal coding region for the pTK (where the native signal is employed). This DNA fragment then is readily inserted proximal to DNA encoding an immunoglobulin light or heavy chain constant region and, if necessary, the resulting construct tailored by deletional mutagenesis. Preferably, the Ig is a human immunoglobulin when the variant is intended for *in vivo* therapy for humans. DNA encoding immunoglobulin light or heavy chain constant regions is known or readily available from cDNA libraries or is synthesized. See for example, Adams *et al.*, Biochemistry 19:2711-2719 [1980]; Gough *et al.*, Biochemistry 19:2702-2710 [1980]; Dolby *et al.*, P.N.A.S. USA, 77:6027-6031 [1980]; Rice *et al.*, P.N.A.S. USA 79:7862-7865 [1982]; Falkner *et al.*, Nature 298:286-288 [1982]; and Morrison *et al.*, Ann. Rev. Immunol. 2:239-256 [1984].

The chimeric proteins disclosed herein are useful as diagnostics for isolating or screening ligands for the pTK of interest using the techniques of Lyman *et al.*, Cell 75:1157-1167 [1993], for example. Also, the chimeric proteins are useful for diagnostic purposes for studying the interaction of various ligands with the extracellular domain of the various pTKs (see, *e.g.*, Bennett *et al.*, J. Biol. Chem. 266(34):23060-23067 [1991]). The chimeric proteins are further useful for the production of antibodies against the extracellular domain of the pTK (see Examples 3 and 5 herein). The chimeric proteins also have an additional therapeutic utility insofar as they provide a soluble form of the extracellular domain of the pTK which generally has an enhanced plasma half life (compared to the extracellular domain only) and therefore can be formulated in a pharmaceutically acceptable carrier and administered to a patient. The chimeric proteins are believed to find use as therapeutic agents for removal of excess systemic or tissue-localized pTK ligand which has been administered to a patient. Removal of excess ligand is particularly desirably where the ligand may be toxic to the patient. The chimeric protein acts to bind the ligand in competition with the endogenous pTK in the patient. Similarly, it is contemplated that the chimeric protein can be administered to a patient simultaneously, or subsequent to, administration of the ligand in the form of a sustained release composition. The chimeric protein acts as a soluble

binding protein for the ligand, thereby extending the half-life of the ligand.

The term "antibody" is used herein in the broadest sense and specifically covers polyclonal antibodies, monoclonal antibodies, immunoglobulin chains or fragments thereof, which react immunologically with a pTK.

In the preferred embodiment of the invention, the antibodies are monoclonal antibodies produced using techniques which are well known in the art. For example, the hybridoma technique described originally by Kohler and Milstein, Eur. J. Immunol., 6:511 [1976], and also described by Hammerling *et al.*, In: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 [1981] can be used. The techniques of Cote *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies [Cote *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 [1985] and Boerner *et al.*, J. Immunol., 147(1):86-95 [1991]).

The term "monoclonal antibody" as used herein refers to an antibody (as hereinabove defined) obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they can be synthesized by a hybridoma culture, uncontaminated by other immunoglobulins.

"Humanized" forms of non-human (*e.g.*, murine) antibodies are immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal amino acid residues derived from a non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced

by corresponding non-human FR residues. Furthermore, a humanized antibody may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance.

The monoclonal antibodies herein include hybrid (chimeric) and recombinant antibodies produced by splicing a variable (including hypervariable) domain of an anti-pTK antibody with a constant domain (*e.g.*, "humanized" antibodies), only one of which is directed against a pTK, or a light chain with a heavy chain, or a chain from one species with a chain from another species, or fusions with heterologous proteins, regardless of species of origin or immunoglobulin class or subclass designation, so long as they are able to bind to the pTK of interest [See, *e.g.*, Cabilly, *et al.*, U.S. Patent No. 4,816,567; and Mage & Lamoyi, in Monoclonal Antibody Production Techniques and Applications, pp.79-97 (Marcel Dekker, Inc., New York [1987]).

For "chimeric" and "humanized" antibodies see, for example, U.S. Patent No. 4,816,567; WO 91/09968; EP 452,508; and WO 91/16927.

Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

In the most preferred embodiment of the invention, the antibodies are agonist antibodies. By "agonist antibody" is meant an antibody which is able to bind to, and activate, a particular pTK. For example, the agonist may bind to the extracellular domain of the pTK and thereby cause dimerization of the pTK, resulting in transphosphorylation and activation of the intracellular catalytic kinase domain. Consequently, this may result in stimulation of growth and/or differentiation of cells expressing the receptor *in vitro* and/or *in vivo*. The agonist antibodies herein are preferably against epitopes within the extracellular domain of the pTK, and preferably have the same biological characteristics as the monoclonal antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession No. ATCC HB 11,583. By "biological characteristics" is meant the *in vitro* and/or *in vivo* activities of the monoclonal antibody, *e.g.*, ability to activate the kinase domain of a particular pTK, ability to stimulate cell growth and/or differentiation of cells expressing the pTK, and binding characteristics of the antibody, etc. Accordingly, the antibody preferably binds to substantially the same

epitope as the anti-HpTK5 monoclonal antibody specifically disclosed herein. Most preferably, the antibody will also have substantially the same or greater antigen binding affinity of the anti-HpTK5 monoclonal antibody disclosed herein. To determine whether a monoclonal antibody has the same specificity as the anti-HpTK5 antibody specifically disclosed (*i.e.*, the antibody having the ATCC deposit No. HB 11,583), one can, for example, use a competitive ELISA binding assay.

DNA encoding the monoclonal antibodies useful in the method of the invention is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells.

The agonist antibodies disclosed herein are useful for *in vitro* diagnostic assays for activating the pTK receptor of interest. This is useful in order to study the role of the receptor in cell growth and/or differentiation.

The pTK agonist antibodies have a further therapeutic utility in a method for enhancing cell growth and/or differentiation comprising administering to a human patient in need of such treatment a physiologically effective amount of an exogenous pTK agonist antibody. Agonist antibodies to the SAL-S1 pTK may find utility in treating bleeding disorders and anemias, since this pTK was found to be expressed in megakaryocytic cells. The bpTK agonist antibodies may similarly be used to enhance differentiation and/or proliferation of brain cells in neurodegenerative diseases (such as Alzheimers disease) based on the expression of these receptors in brain tissue. Finally, HpTK5 agonist antibodies may be used to enhance proliferation of primitive hematopoietic cells in patients having undergone chemo- or radiation therapy or bone marrow transplantation.

An "exogenous" therapeutic compound is defined herein to mean a therapeutic compound that is foreign to the mammalian patient, or homologous to a compound found in the mammalian patient but produced outside the mammalian patient.

The antibodies of the present invention are also suitable for detecting a pTK by contacting a source suspected to contain the pTK with a detectably labeled monoclonal antibody, and determining whether the antibody binds to the source. There are many different labels and methods of labeling known in the art. Suitable labels include, for example, enzymes, radioisotopes, fluorescent compounds, chemi- and bioluminescent compounds, paramagnetic isotopes. The pTK may be present in biological samples, such as biological fluids or tissues. For analytical or diagnostic purposes, the antibodies of the present invention are administered in an amount sufficient to enable the detection of a site on a pTK for which the monoclonal antibody is specific. The concentration of the detectably labeled monoclonal antibody should be sufficient to give a detectable signal above background, when bound to a pTK epitope.

The pTK agonist antibodies disclosed herein may be administered to a mammal, preferably a human, in a pharmaceutically acceptable dosage form, including those that may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

Such dosage forms encompass pharmaceutically acceptable carriers that are inherently nontoxic and nontherapeutic. Examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of antibody include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, and sublingual tablets. The antibody will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

Pharmaceutical compositions may be prepared and formulated in dosage forms by methods known in the art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition 1975.

An effective amount of the pTK agonist antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. A typical daily dosage might range from about 1 μg/kg to up to 1000 mg/kg or more, depending on the factors mentioned above. Typically, the clinician will administer the molecule until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

Depending on the type and severity of the disease, from about 0.001 mg/kg to about 1000 mg/kg, more preferably about 0.01 mg to 100 mg/kg, more preferably about 0.010 to 20 mg/kg of the agonist antibody might be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs or the desired improvement in the patient's condition is achieved. However, other dosage regimens may also be useful.

The present invention will now be illustrated by the following Examples, which are not intended to be limiting in any way. The disclosures of all literature references cited in the specification are expressly incorporated herein by reference.

EXAMPLE 1

IDENTIFICATION AND ISOLATION OF pTK GENES

To facilitate the isolation and identification of these novel pTK genes, two sets of DNA probes were generally used (see Table 1).

The first set consisted of two degenerate oligonucleotide sequences, pTK 1 (SEQ ID NO: 1) and pTK 2 (SEQ ID NO: 2). These sequences were used as polymerase chain reaction (PCR) primers, using standard PCR techniques, to amplify tyrosine kinase DNA segments.

The second set consisted of two oligonucleotide sequences, pTK 3 (SEQ ID NO: 3) and pTKKW (SEQ ID NO: 4) selected from the highly conserved regions of the catalytic domains of the c-kit subgroup of protein tyrosine kinases. These sequences were also used as polymerase chain reaction primers in a second round of DNA amplification. Using this two-step amplification procedure, DNA fragments which hybridized to these pTK primers were identified, isolated and subsequently sequenced using known laboratory techniques.

TABLE 1

First Round of Amplification

Probe name	Sequence
pTK1	5'-CGGATCCACAGNGACCT-3'
pTK2	5'-GGAATTCCAAAGGACCAGACGTC-3'

Second Round of Amplification

pTK3	(kit family specific)	5'-CGGATCCATCCACAGAGATGT-3'
pTKKW	(kit family specific)	5'-GGAATTCCTTCAGGAGCCATCCACTT-3'

EXAMPLE 2

ISOLATION AND CHARACTERIZATION OF HpTK5

A. DNA Amplification and Cloning of HpTK5

Light density human bone marrow mononuclear cells, obtained from normal volunteers using Deaconess Hospital Institutional Review Board approved protocols and with voluntary written informed consent, were separated by anti-CD34 antibody (AMAC, Westbrook, ME) and immunomagnetic beads (Dynal, Oslo, Norway). Flow cytometric analysis using FITC-conjugated anti-CD34 antibody (AMAC) confirmed ~95% CD34 positivity of isolated cells. The hepatoma cell line, Hep3B, was cultured in alpha medium (Gibco, Grand Island, NY) supplemented with penicillin (100U/mL), streptomycin (100μg/mL) and 10% fetal bovine serum (Gibco) at 37°C in a 5% CO_2 incubator. Total RNA extracted from CD34+ bone marrow mononuclear or Hep3B cells was reverse transcribed with random primers and the Moloney murine leukemia virus reverse transcriptase (RT) following the conditions of the manufacturer (Gibco-BRL) in a 20 μl reaction. PCR was performed on the RT reaction product in a 100μl reaction containing 50mM KCl, 10mM Tris·HCl (pH 8.4), 1.5mM MgCl , 20 μg/ml gelatin, 0.2mM dNTPs,

2.5 units Taq polymerase (Perkin-Elmer/Cetus) and 50pmol each of pTK-specific degenerate primers

[pTK1 5'TCGGATCCACA/CGNGAC/TC/TTGGC 3' (SEQ ID NO. 35),

pTK1B 5'TCGGATCCAC/TC/AGNGAC/TC/TTNGCNGC 3' (SEQ ID NO. 36),

pTK2 5'CTCGAATTCCA/GA/TAA/GC/GT/ACCAG/CACA/GTC 3' (SEQ ID NO. 37),

pTK2B 5'CTCGAATTCCA/GA/TAT/CC/GT/ACCAT/AACA/GTC 3'(SEQ ID NO. 38)] derived from consensus regions among known pTKs as previously reported by others (Hanks *et al.*, Science, 241:42-52 [1988]; Wilks, Proc. Nat. Acad. Sci., USA 86:1603-1607 [1989]; and Matthews *et al.*, Cell 65:1143-1152 [1991]). The PCR cycle was 1.5min at 95°C, 2min at 37°C and 3 min at 63°C repeated 35 times. The reaction product was electrophoretically separated on a 2% low-melting agarose gel, purified on an Elutip-D column (Schleicher & Schuell) digested with EcoR1 and BamH1, and subcloned into pUC19.

Recombinants were sequenced by the Sanger dideoxy method and evaluated by the FASTA nucleic acid sequence analysis program. One clone termed HpTK5 (214 bp) was radiolabelled by random priming and used to screen an oligo dT-primed lambda gt10 Hep3B cDNA library. DNA was isolated from 17 positive phage plaques and inserts were subcloned into the EcoR1 site of pBluescript (Stratagene La Jolla, CA). The largest insert, a 3969 bp cDNA, was sonicated to an average size of 800-2000 bp and cloned into the Sma1 site of M13. Overlapping clones were sequenced using the Taq Dye Primer Cycle Method (CABI) on the Catalyst 800 Molecular Biology Lab Station (ABI). Sequencing reactions were then analyzed on the ABI 373A Automated DNA Sequenator.

A single full-length 3969 bp cDNA was isolated and sequenced. (Figures 8A-8F). The full length clone, named hepatoma transmembrane kinase (HTK) or HpTK5, included an open reading frame extending from nucleotide 90 to 3050 predicted to encode a 987 amino acid protein of 108,270 Dalton. The putative initiation codon is preceded by an in-frame stop codon beginning at base 78. Preceding the open reading frame is a 5' untranslated region which is GC-rich as is characteristic for many growth factors or growth factor receptors (Kozak, J. Cell Biol. 115:887-903 [1991]).

The predicted protein sequence includes a transmembrane region (aa 538-563) which divides HpTK5 into extracellular (ECD) and intracellular domains (ICD). The ECD of 538 amino acids includes a signal peptide of 15 amino acids and a cysteine-rich box containing 20 Cys residues. In

addition, there are two fibronectin type III repeats spanning aa 321 to 425 and 435 to 526. Asn at positions 208, 340 and 431 are possible sites for N-glycosylation.

The putative intracellular domain (ICD) contains a kinase consensus region from position 613 through 881. This kinase region includes a putative ATP-binding consensus (Gly-X-Gly-X-X-Gly) in subdomain I at positions 622-627. A Lys at position 647 (subdomain II) corresponds to an invariant Lys among tyrosine kinases thought to be critical for the phosphotransfer reaction. Signature regions indicative of substrate specificity suggest that HpTK5 is a tyrosine rather than a serine/threonine kinase. These include the sequence at positions 740-745 in subdomain VI and the sequence at positions 783-790 in subdomain VIII. Tyrosine residues at positions 601, 619 and 741 are possible substrates for tyrosine kinase activity.

The predicted amino acid sequence of HpTK5 most closely resembles that of the subfamily originally defined by *EPH*. The pattern of expression of the *EPH* subfamily is suggestive of a role in differentiation and development. In particular, the emergence of neural elements corresponds with the expression of certain *EPH*-related genes. The *EPH* family receptors, Hek2 and Elk, are the most closely related pTKs to HpTK5. They share 79.3 and 76.5% identity within the ICD respectively and 45 and 42% identity within the ECD respectively.

B. Chromosome Mapping of HpTK5

Somatic cell hybrid DNAs from a panel of 25 human-hamster cell lines (Bios, New Haven, CN) were used for chromosome localization by PCR. Two sets of primers from the 3' untranslated region of HpTK5 were chosen. PCR was performed with 250 ng DNA and 50 pmol each of the 5' and 3' primers, 50 mM KCl, 1.5mM $MgCl_2$, 20 μg/ml gelatin, 0.2 mM dNTPs and 2.5 units Taq polymerase in a final volume of 100 μl. Cycles of 94°C for 30 sec, 60°C for 30 sec and 72°C for 30 sec were repeated 30 times. A portion of each sample (15 μl) was electrophoresed through a 1.5% agarose gel, transferred to a nylon membrane and hybridized to a ^{32}P-labelled full length HpTK5 cDNA probe prior to 5 hour autoradiography. Positives were scored and compared to a matrix summary of human chromosomal material present in each of the somatic cell hybrid DNAs.

The 3'-untranslated region characteristically contains few, if any, intervening sequences and has a high degree of diversity among members

of gene families making it preferred in this type of analysis. Both sets of primers gave results that were consistent with human chromosome 7 only. Human chromosome 7 also includes the genes for the EGF receptor, hepatocyte growth factor (HGF) receptor, HGF, platelet-derived growth factor (PDGF) and interleukin-6. Karyotypic abnormalities involving this chromosome are common among human leukemias, particularly in aggressive myeloid leukemias that occur following radiation, alkylating agent chemotherapy or a pre-existing myelodysplastic condition (Baer *et al.*, Curr. Opin. Oncol. 4:24-32 [1992]).

C. Northern Blotting of HpTK5

Poly-A selected RNA was electrophoresed through a 1.2% agarose, 2.2M formaldehyde gel and transferred to a nylon filter. Prepared or commercially obtained filters were hybridized in 50% formamide at 42°C to ^{32}-P labeled HpTK5, glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) or actin cDNA inserts and washed under stringent conditions (final wash: 0.1 x SSC, 0.2% SDS at 65°C). SSC is 0.15 M NaCl/ 0.015M Na_3·citrate, pH 7.6. Northern blots of human fetal or adult tissue RNA were obtained from Clontech (Palo Alto, CA) and contained 2 μg/lane of poly A selected RNA.

Northern blot analysis of human fetal tissues revealed a single transcript of ~4Kb in heart, lung, liver and kidney, with a lesser signal detectable in brain. In adult human tissue, no signal was detectable in brain, while placenta had a particularly intense signal followed by kidney, liver, lung and pancreas. Skeletal muscle and heart were of lower signal intensity.

HpTK5 expression in human tumor cell lines was also analyzed by Northern blot analysis performed as discussed above. Cell lines derived from liver, breast (MCF 7), colon (Colo 205), lung (NCI 69), melanocyte (HM-1) or cervix (HeLa) had detectable signal of appropriate size. Message was present in select cell lines of hematopoietic origin. K562 (a primitive myeloid cell with multipotential), THP-1 (a monocytoid cell), U937 (a myelomonocytic cell line), Hep3B (a human hepatocarcinoma cell line), and CMK (of megakaryocytic origin) were all positive for HpTK5 message, but lymphoid (H9, Jurkat, JH-1, Raji, Ramos) or select other myeloid cells (KG-1 or KMT2) had no detectable transcript by Northern analysis.

Differential expression of the HpTK5 transcript in fetal versus adult brain suggests that HpTK5 may share, with other *EPH* subfamily

members, a role in events related to neural development. However, unlike some members of the *EPH* subfamily which are exclusively expressed in neurons (Maisonpierre *et al.*, *supra*), HpTK5 is widely expressed in other tissues. In particular, HpTK5 is expressed in hematopoietic cells including CD34+ hematopoietic progenitor cells. The presence of the HpTK5 message in early hematopoietic cells and cell lines of myeloid lineage, but not in cell lines derived from lymphoid cells, suggests that HpTK5 may have lineage restricted expression.

EXAMPLE 3

PRODUCTION OF POLYCLONAL ANTIBODIES TO HPTK5

An HpTK5 extracellular domain (ECD)-human IgG_1 Fc fusion gene was constructed and fusion protein produced as previously described (Bennett *et al.*, J. Biol. Chem. 266:23060-23067 [1991]). Polyclonal antibodies were generated in New Zealand White rabbits against the fusion protein; 4μg in 100μL PBS was emulsified with 100μL Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). For the primary immunization and the first boost, the protein was injected directly into the popliteal lymph nodes (Sigel *et al.*, Methods Enzymol. 93:3-12 [1983]). For subsequent boosts, the protein was injected into subcutaneous and intramuscular sites. 1.3 μg protein/kg body weight was injected every 3 weeks with bleeds taken 1 and 2 weeks following each boost. HpTK5 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of NIH3T3 cells transfected with full length HpTK5 or vector alone using a 1:200 dilution of pre-immune serum or anti-HpTK5-IgG Fc serum. Significant peak shifts were observed in several HpTK5 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 4

UTILITY AND AGONIST ACTIVITY OF POLYCLONAL ANTIBODIES TO HPTK5

A. FLAG-HpTK5 Fusion Construct

Overlapping oligonucleotides encoding a 12 amino acid peptide having the sequence MDYKDDDDKKLAM (SEQ ID NO: 39) which includes the 4 amino acid antibody recognition site "FLAG" (IBI, New Haven, CT) a 5'-EcoRV restriction site and a 3'-NcoI restriction site

(5'-CCGGATATCATGGACTACAAGGACGACGATGACAAGAAGCTTGCCATGGAGCTC; SEQ ID NO: 40), were ligated into the NcoI site (base 88) of HpTK5 in the EcoRV digested Bluescript (Stratagene, La Jolla, CA) vector.

B. *In vitro* Transcription and Translation

Transcription was performed on 2 pmol of linearized HpTK5 or FLAG-HpTK5 containing plasmid at 37°C for 1 h in 50 µl volume containing 10 mM dithiothreitol, 2.5 µg bovine serum albumin, 0.25 mM each dNTP, 0.5 M m7GRNA cap (New England Biolabs, Beverly, MA), 2.5 units RNasin (Promega, Madison, WI), 3 units T3 RNA polymerase (Pharmacia, Piscataway, NJ). 1 µg of DNAase (New England Biolabs, Beverly MA) was added for 15 min at 37°C prior to phenol/chloroform extraction and ethanol precipitation. Translation was performed using the Promega rabbit reticulocyte lysate kit according to the manufacturer's specifications with or without ^{35}S-methionine (350 µCi) labeling. Sample buffer containing SDS and beta-mercaptoethanol (2-ME) was added before boiling and 10% SDS-PAGE.

C. HpTK5 Expression in NIH3T3 Cells

A 4038 bp ClaI - XbaI cDNA fragment containing 32 bp of linker sequence, 37 bp of pBluescript (Stratagene La Jolla, CA) polylinker and the entire 3969 bp HpTK5 cDNA was subcloned into the expression vector pRIS (Genentech, Inc.) under the control of the Rous sarcoma virus LTR promoter. NIH3T3 cells maintained in high glucose Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FCS were co-transfected with pRIS-HpTK5 and pNeo (an SV40 based vector containing the neomycin resistance marker) by the calcium phosphate method as described by Gorman *et al.*, in DNA Prot. Engineer. Tech. 2:3-10 [1990]. Neomycin resistant colonies were selected 48 hours after transfection with Geneticin (Gibco/BRL) at 400 µg/ml. Fourteen days later individual resistant colonies were isolated, expanded and analyzed by flow cytometry for HpTK5 expression using rabbit polyclonal antiserum.

D. Immunoprecipitation

Cells (Hep3B, control NIH3T3 or HpTK5 transfected NIH3T3) or *in vitro* translated protein (HpTK5 or FLAG-HpTK5) were used for immunoprecipitation with either serum (pre-immune or anti-HpTK5-IgG Fc) or monoclonal antibody (FLAG-specific, M2, or isotype control) (IBI,

Rochester, NY). Subconfluent cells were labeled with 200μCi/ml ^{35}S-methionine for 18 hours and lysed in lysis buffer (150 mM NaCl, 50 mM Tris-HCl pH8.0, 1 mM EDTA, 0.025 Na azide, 1% NP-40, 0.1% SDS, 10% Glycerol, 0.5% Na deoxycholate, 1 mM phenylmethylsulfonyl flouride (PMSF), 10 μg/ml aprotinin, 10 μg/ml leupeptin and 50 μM Na vanadate) for 30 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C. Cell lysate supernatant or *in vitro* translation mixture was precleared with 0.05 volume of normal rabbit serum and adsorbed with 0.05 volume of Staphylococcus aureus protein-A Sepharose CL4B. After centrifugation, preimmune or immune serum (1:100 dilution), or monoclonal antibody, was added and rocked overnight at 4°C before 100 μl of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 95°C for 5 min and analyzed by 7.5% SDS-PAGE.

E. Cell Fractionation

Cell fractionation of Hep3B cells was performed to confirm the membrane localization of HpTK5 predicted by its amino acid sequence. Hep-3B cells (1x10^7) were labeled with 200μCi/ml ^{35}S-methionine in alpha MEM medium containing 10% dialyzed FCS overnight. The cells were washed twice with cold PBS, scraped into 1ml of cold buffer (20mM Tris-HCl pH 7.5, 2mM EDTA, 5mM EGTA, 0.25M sucrose, 0.01% leupeptin, 4mM PMSF, 10mM 2-ME) and disrupted by sonication for 40 seconds. Whole homogenates were centrifuged at 12,000 X g for 15 min, the nuclear pellets isolated and the decanted supernatant centrifuged at 140,000 X g for 40 min at 4°C to pellet membranes. The resultant supernatant served as the cytosolic (C) fraction. Nuclear (N) and membrane (M) fractions were washed and dissolved in buffer containing 0.5% NP-40 prior to immunoprecipitation. The C, N or M fractions were immunoprecipitated with an anti-HpTK5 or pre-immune (control) serum, subjected to 12% SDS-PAGE and autoradiographed. HpTK5 segregated predominantly with the membrane fraction, though immunoprecipitated material was evident to a lesser extent in cytosol.

F. Protein Kinase Assay

Immunoprecipitates were washed once with kinase buffer (25mM Hepes pH7.4, 1mM DTT, 10mM MgCl, 10mM MnCl), and resuspended in 40μl of kinase

buffer containing either unlabeled ATP or 10μCi of ^{32}P-ATP (3000Ci/mM). After a 10min incubation at 30°C, the reaction was stopped by adding 40μl of 2 X sample buffer and boiling the samples for 3min prior to electrophoresis on 8.0% SDS-PAGE gel. The dried gel was covered with 4 sheets of aluminum foil to block ^{35}S-labelled protein autoradiography and the gel was placed under film for 5 hours to overnight.

G. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 μm nitrocellulose (Bio-Rad) or a 0.45μm polyvinylidene diflouride (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:7500 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$) plus BCIP, NBT substrates.

H. Antibody Induced Phosphorylation Assay

Rabbit antisera to HpTK5-IgG Fc were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 1 hour prior to adding pre-immune or immune serum at a 1:50 dilution for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to polyclonal antiserum showing an agonist-like effect of antibody binding. Interaction of HpTK5 with an antibody directed against its ECD induces phosphorylation. This provides

further support that HpTK5 may serve as a receptor for a ligand that triggers kinase activation. Details of the signaling pathway of HpTK5 may be further explored using antisera as a surrogate ligand.

I. Conclusions

An HpTK5 ECD-IgG Fc fusion protein was expressed, purified and used to generate rabbit anti-serum which immunoprecipitated a 120kD protein from Hep3B cells. The specificity of the antiserum was confirmed by immunoprecipitation of *in vitro* translated HpTK5 RNA and HpTK5 transfected NIH3T3 cells. To determine the functional capacity of HpTK5, *in vitro* translated HpTK5 was immunoprecipitated, exposed to kinase conditions and immunoblotted using a phosphotyrosine specific monoclonal antibody. The data obtained indicated that HpTK5 is phosphorylated on tyrosine. However, the presence of other bands consistently appearing in the ^{32}P-labelled immunoprecipitation suggested that HpTK5 protein was only partially purified and therefore, it could not be concluded that HpTK5 was enzymatically active. To overcome this problem, a fusion construct was generated in which an 8 amino acid epitope (FLAG) was added to the N-terminus of HpTK5. The FLAG-HpTK5 fusion was *in vitro* translated and immunoprecipitated with a FLAG-specific monoclonal antibody resulting in a single protein of appropriate size (~120kD). When subjected to kinase conditions in the presence of ^{32}P-ATP, the HpTK5-FLAG fusion protein was labelled on tyrosine confirming tyrosine autophosphorylation and thereby, the kinase function of HpTK5.

EXAMPLE 5

PRODUCTION OF MONOCLONAL ANTIBODIES TO HPTK5

Anti-HpTK5 monoclonal antibodies were produced by hyperimmunizing BALB/c mice intraperitoneally with the HpTK5 extracellular domain (ECD)-human IgG_1 Fc fusion protein (produced using the techniques disclosed above) in RIBI adjuvant (RIBI ImmunoChem Research, Hamilton, MT) and fusing splenocytes with the mouse myeloma cell line X63-Ag8.653 (Kearney *et al.*, J. Immunol. 123:1548-1550 [1979]). The antibodies were purified from ascites fluid using protein A-Sepharose (Repligen Corp., Cambridge, MA) and established affinity chromatography methods (Goding, J.W., J. Immunol. Methods 20:241-253 [1978]).

Monoclonal antibodies were screened for their ability to bind the HpTK5 antigen. Starting on day 15 post fusion, culture supernatants were

harvested from the fusion plates and assayed for their ability to specifically "capture" HpTK5-IgG. In this ELISA assay, goat anti-mouse IgG was coated onto 96 well microtiter plates. The culture supernatants (100μl) were added to the wells and the mouse IgG present was bound by the goat anti-mouse IgG antibodies. The plates were washed and either HpTK5-IgG or CD4-IgG (100μl at 6nM) was added. The "captured" immunoadhesin was detected using a goat anti-hu (Fc specific) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490nm.

Agonist antibodies were then screened for using the techniques disclosed in Example 6 below. Two agonist monoclonal antibodies were identified, one of which has been deposited with the ATCC.

EXAMPLE 6

AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO HPTK5

The monoclonal antibodies produced using the techniques disclosed in Example 5 were tested for their ability to induce HpTK5 phosphorylation in HpTK5 transfected NIH3T3 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 1 hour prior to adding pre-immune serum or anti-HpTK5 monoclonal antibody (undiluted conditioned hybridoma media was used) for 30 minutes. Cells were then washed in PBS and lysed in either 2X sample buffer or NP-40 lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. HpTK5 expressing cells were exposed to the monoclonal antibody and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of HpTK5 was observed following exposure to monoclonal antibodies showing an agonist-like effect of antibody binding. Accordingly, interaction of HpTK5 with a monoclonal antibody directed against its ECD is able to induce phosphorylation of the kinase domain thereof.

EXAMPLE 7

PRODUCTION OF POLYCLONAL ANTIBODIES TO SAL-S1

A SAL-S1 extracellular domain (ECD)-human IgG_1 Fc fusion gene was constructed and fusion protein produced as previously described in

Bennett *et al.*, J. Biol. Chem. 266:23060-23067 [1991]. Briefly, PCR primers otk 1.41.1 (SEQ ID NO: 43) and otk 1.41.2 (SEQ ID NO: 44) were employed in the PCR technique using plasmid pRK5.tk1-1.1 (SEQ ID NO: 45) containing SAL-S1 nucleic acid as a template to create a DNA fragment which, when digested with SalI/BstEII, generated an 155bp SalI/BstEII fragment. This 155bp fragment was combined with a 6839bp SalI/HindIII fragment isolated from pRK5.tk1-1.1 and a 719 bp BstEII/HindIII fragment isolated from pBSSK-CH2-CH3 (Bennett *et al.*, *supra*). These fragments were ligated together to create a plasmid pRK5.tk1.ig1.1 (7713bp in size) which, when transfected into 293 cells, was used to produce a SAL-S1 extracellular domain (ECD)-human IgG Fc fusion protein. Fusion protein was prepared and purified as described in Bennett *et al.*, *supra*. Polyclonal antibodies were generated in female New Zealand White rabbits against the fusion protein. Briefly, 12.5μg of fusion protein in 0.625ml PBS was emulsified with 0.625ml Freund's adjuvant (complete adjuvant for the primary injection and incomplete adjuvant for all boosts). The primary injection and all boosts were intramuscular at two sites and subcutaneous at multiple sites. Boosts were carried out at 3 week intervals with bleeds taken 1 and 2 weeks following each boost. SAL-S1 specificity of the immunized rabbit serum was assessed by flow cytometric analysis of 293 (ATCC CRL 1593) and COS7 (ATCC CRL 1651) cells transfected with full length SAL-S1 or vector alone (see below) using a 1:200 dilution of pre-immune serum or anti-SAL-S1-IgG Fc serum. Significant peak shifts were observed in several SAL-S1 expressing clones as compared to either pre-immune serum or vector alone transfectant controls.

EXAMPLE 8

UTILITY AND AGONIST ACTIVITY OF SAL-S1 POLYCLONAL ANTIBODIES

A. Immunoprecipitation

Control 293 and COS7 cells as well as SAL-S1 transfected 293 and COS7 cells were used for immunoprecipitation with either pre-immune serum or anti-SAL-S1-IgG Fc polyclonal antibody. COS7 and 293 cells were transfected using a $CaPO_4$ procedure as described by Gorman, C. DNA Cloning, Glover D. Ed., IRL Press, Oxford, vol2: 143-190 (1985). For transient expression, 293 cells were transfected as described by Gearing *et al.* EMBO 8: 3667-3676 (1989). Subconfluent cells were labeled with 200μCi/ml ^{35}S- methionine for 18 hours and lysed in lysis buffer (150 mM

NaCl, 50mM HEPES, pH 7.5, 1 mM EGTA, 0.025 Na azide, 1% Triton-X 100, 1.5mM $MgCl_2$, 10% Glycerol, 1 mM phenylmethylsulfonyl flouride [PMSF], 10 μg/ml aprotinin, 10 μg/ml leupeptin and 50 μM Na vanadate) for 10 min on ice. The cell lysate was centrifuged (12,000 X g) for 10 min at 4°C. After centrifugation, preimmune or polyclonal antibody was added to the supernatant and rocked for 4 hrs at 4°C before 100 μl of protein-A Sepharose CL4B was added and the solution rocked 4°C for additional 2 h. Immunoprecipitates were washed, suspended in SDS/PAGE loading buffer (10% glycerol, 5% 2-ME, 2.3% SDS and 62.5mM Tris-HCl pH 6.8), heated to 95°C for 5 min and analyzed by 7.5% SDS-PAGE.

B. Western Blotting and Phosphotyrosine Assay

Proteins were electrophoretically transferred to a 0.2 μm nitrocellulose (Bio-Rad) or a 0.45μm polyvinylidene diflouride (Millipore) membrane in a buffer containing 25 mM Tris-HCl (pH 7.5), 192 mM glycine and 20% methanol at 100 mA for 2 h. Filters were washed in TBS (10 mM Tris-HCl pH 8.0, 150 mM NaCl) blocked by incubating in TBST (TBS with 0.05% Tween-20) plus 5% BSA overnight. Filters were washed four times for 5 min each in TBST and incubated for 2 h with 4G10 anti-phosphotyrosine antibody from UBI (1:1000 dilution in TBST). Filters were washed four times for 5 min each in TBST and incubated for 1 h with the alkaline phosphatase labelled anti-mouse secondary antibody (Promega) at a 1:5000 dilution in TBST. After washing four times, the blot was developed for 30-60 min in AP buffer (100mM Tris-HCl, 100 mM NaCl, 5 mM $MgCl_2$) plus BCIP, NBT substrates.

C. Antibody Induced Phosphorylation Assay

Rabbit antisera to SAL-S1-IgG Fc were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were plated at a density of 5 x 10^5 cells/well in a 6-well plate and, after 24 hours, were serum starved for 12 hours prior to adding pre-immune or immune serum at a 1:5 dilution for 30 minutes. Cells were then washed in PBS and lysed in either sample buffer or Triton-X lysis buffer as described above. Either crude lysates or immunoprecipitated cell lysates were then separated via 8% or 4-12% gradient SDS-PAGE and analyzed by anti-phosphotyrosine immunoblot as described above. SAL-S1 expressing cells were exposed to antisera and separated by SDS-PAGE either with or without immunoprecipitation. The electrotransferred gel was immunoblotted

with anti-phosphotyrosine antibody. Enhanced tyrosine phosphorylation of SAL-S1 was observed following exposure to polyclonal antiserum showing an agonist-like effect of antibody binding. Interaction of SAL-S1 with an antibody directed against its ECD induces phosphorylation.

EXAMPLE 9

PRODUCTION OF MONOCLONAL ANTIBODIES TO SAL-S1

Anti-SAL-S1 monoclonal antibodies were produced by hyperimmunizing BALB/c mice in the foot pad with the SAL-S1 extracellular domain-human IgG_1 Fc fusion protein in RIBI adjuvant (RIBI Immunochem Research, Hamilton, MT) and fusing lymphocyte from lymph nodes with the mouse myeloma cell line X63-Ag8U1.

Starting on day 10 post fusion, cultured supernatants were harvest from the fusion plates and assayed for their ability to bind to SAL-S1. In this ELISA assay, SAL-S1 IgG_1 was coated onto 96 microtiter plates. The cultured supernatants (100μl) were added to the wells and the mouse antibodies present were bound to Sal-S1 IgG_1. The plates were washed and mouse IgG was detected using a goat anti-mouse IgG (Fc specific with no cross reactivity against human IgG Fc) horseradish peroxidase conjugate and orthophenylene diamine substrate. Quantitation of substrate catalysis was determined by optical density at 490 nm.

Cultured supernatants which were positive from ELISA were then tested for their ability to specifically bind to 293 transfected with SAL-S1 receptor and analyzed by flow cytometry. Agonist antibodies were then screened for using the techniques disclosed in Example 10 below. Six agonist monoclonal antibodies were identified.

EXAMPLE 10

AGONIST ACTIVITY OF MONOCLONAL ANTIBODIES TO SAL-S1

The monoclonal antibodies were tested for their ability to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells. Cells were harvested from tissue culture dish by assay buffer and washed 2x with the same buffer. $1x10^5$ cells were added to a 96 U-bottom plate which was centrifuged and assay buffer was removed. 150 μl of cultured supernatants was added to each well followed by incubation at 37°C for 30 minutes, the plate was centrifuged and cultured supernatants were removed. 100 μl of Fixing solution was added, the cells were fixed for 30 minutes at -20°C, cells were washed with buffer 2x and stained with anti-phosphotyrosine

conjugate with FITC for 60 minutes at 4°C. Cells were analyzed by flow cytometry (FACScan Becton Dickinson, milplitas, CA). The six anti-SAL-S1 monoclonal antibodies were able to induce SAL-S1 phosphorylation in SAL-S1 transfected 293 cells.

Deposit of Materials

The following culture has been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, USA (ATCC):

Hybridoma	ATCC No.	Deposit Date
Anti-HpTK5	HB 11,583	March 15, 1994

This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture for 30 years from the date of deposit. The organism will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if the culture on deposit should die or be lost or destroyed when cultivated under suitable conditions, it will be promptly replaced on notification with a viable specimen of the same culture. Availability of the deposited strain is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the culture deposited, since the deposited embodiment is intended as a single illustration of one aspect of the invention and any culture that are functionally equivalent

are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustration that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Genentech, Inc.
Bennett, Brian D.
Goeddel, David
Lee, James M.
Matthews, William
Tsai, Siao Ping
Wood, William I.

(ii) TITLE OF INVENTION: PROTEIN TYROSINE KINASE AGONIST ANTIBODIES

(iii) NUMBER OF SEQUENCES: 45

(iv) CORRESPONDENCE ADDRESS:
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(B) STREET: 460 Point San Bruno Blvd
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: patin (Genentech)

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/222616
(B) FILING DATE: 04-APR-1994

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Wendy M. Lee
(B) REGISTRATION NUMBER: 00,000
(C) REFERENCE/DOCKET NUMBER: 821P3PCT

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 415/225-1994
(B) TELEFAX: 415/952-9881
(C) TELEX: 910/371-7168

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGGATCCACA GNGACCT 17

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GGAATTCCAA AGGACCAGAC GTC 23

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGATCCATC CACAGAGATG T 21

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGAATTCCTT CAGGAGCCAT CCACTT 26

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 bases
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GGATCCTGTG CATCAGTGAC TTAGGGCTAG GAACATTCTG CTGTCGGAAA 50

GCGACGTGGT GAAGATCTGT GACTTTGGCC TTGCCCGGGA CATCTACAAA 100

GACCCCAGCT ACGTCCGCAA GCATGCCCGG CTGCCCCTGA AGTGGATGGC 150

GCCAGAATTC 160

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Asp Pro Val His Gln Xaa Leu Arg Ala Arg Asn Ile Leu Leu Ser
1 5 10 15

Glu Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp
20 25 30

Ile Tyr Lys Asp Pro Ser Tyr Val Arg Lys His Ala Arg Leu Pro
35 40 45

Leu Lys Trp Met Ala Pro Glu Phe
50 53

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 147 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGATCCATTC ACAGAGACCT AGCAGCACGC AACATCCTGG TCTCAGAGGA 50

CCTGGTAACC AAGGTCAGCG ACTTTGGCCT GGCCAAAGCC GAGCGGAAGG 100

GGCTAGACTC AAGCCGGCTG CCCGTCAAAT GGATGGCTCC CGAATTC 147

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gly Ser Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ser
1 5 10 15

Glu Asp Leu Val Thr Lys Val Ser Asp Phe Gly Leu Ala Lys Ala
20 25 30

Glu Arg Lys Gly Leu Asp Ser Ser Arg Leu Pro Val Lys Trp Met
35 40 45

Ala Pro Glu Phe
49

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 149 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GTTGGAATTC CTTCCGGCGC CATCCATTTC ACCGGCAGCT TTATTTCGTG 50

TCTAGATTCA TAGATGTCTT CATTATCTAC CTTAAAAACT CTGGCAAGTC 100

CAAAATCTGC TACTTTGTAG ATATTATGTT CACCAACGAG GACATTCCT 149

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Val Gly Ile Pro Ser Gly Ala Ile His Phe Thr Gly Ser Phe Ile
1 5 10 15

Ser Cys Leu Asp Ser Met Ser Ser Leu Ser Thr Leu Lys Thr Leu
20 25 30

Ala Ser Pro Lys Ser Ala Thr Leu Ile Leu Cys Ser Pro Thr Arg
35 40 45

Thr Phe
47

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GTGCACAGGG ATCTCGCGGC TCGGAACATC CTCGTCGGGG AAAACACCCT 50

CTCGAAAGTT GGGGACTTCG GGTTAGCCAG GCTTATCAAG GAGGACGTCT 100

ACCTCTCCCA TGACCACAAT ATCCCCTACA AATGGATGGC CCCTGAGGGA 150

A 151

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn
1 5 10 15

Thr Leu Ser Lys Val Gly Asp Phe Gly Leu Ala Arg Leu Ile Lys
20 25 30

Glu Asp Val Tyr Leu Ser His Asp His Asn Ile Pro Tyr Lys Trp
35 40 45

Met Ala Pro Glu Gly
50

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 137 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTTCACCGAG ATCTCAAGTC CAACAACATT TTGCTGCTGC AGCCCATTGA 50

GAGTGACGAC ATGGAGCACA AGACCCTGAA GATCACCGAC TTTGGCCTGG 100

CCCGAGAGTG GCACAAAACC ACACAAATGA GTGCCGC 137

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Val His Arg Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro
1 5 10 15

Ile Glu Ser Asp Asp Met Glu His Lys Thr Leu Lys Ile Thr Asp
20 25 30

Phe Gly Leu Ala Arg Glu Trp His Lys Thr Thr Gln Met Ser Ala
35 40 45

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 211 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCAATCGTG ACCTCGCCGC CGAAATGTG TTGCTAGTTA CCCAACATTA 50

CGCCAAGATC AGTGATTTCG GACTTTCCAA AGCACTGCGT GCTGATGAAA 100

ACTACTACAA GGCCCAGACC CATGGAAAGT GGCCTGTCAA GTGGTACGCT 150

CCGGAATGCA TCAACTACTA CAAGTTCTCC AGCAAAAGCG ATGTCTGGTC 200

CTTTGGAATT C 211

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 70 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Val Asn Arg Asp Leu Ala Ala Arg Asn Val Leu Leu Val Thr Gln
1 5 10 15

His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg
20 25 30

Ala Asp Glu Asn Tyr Tyr Lys Ala Gln Thr His Gly Lys Trp Pro
35 40 45

Val Lys Trp Tyr Ala Pro Glu Cys Ile Asn Tyr Tyr Lys Phe Ser
50 55 60

Ser Lys Ser Asp Val Trp Ser Phe Gly Ile
65 70

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6827 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA GAATAACATC 850

CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

CGAGATCCAT TGTGCTGGCG CGGATTCTTT ATCACTGATA AGTTGGTGGA 1000

CATATTATGT TTATCAGTGA TAAAGTGTCA AGCATGACAA AGTTGCAGCC 1050

GAATACAGTG ATCCGTGCCG CCCTAGACCT GTTGAACGAG GTCGGCGTAG 1100

ACGGTCTGAC GACACGCAAA CTGGCGGAAC GGTTGGGGGT TCAGCAGCCG 1150

GCGCTTTACT GGCACTTCAG GAACAAGCGG GCGCTGCTCG ACGCACTGGC 1200

CGAAGCCATG CTGGCGGAGA ATCATAGCAC TTCGGTGCCG AGAGCCGACG 1250

ACGACTGGCG CTCATTTCTG ACTGGGAATG CCCGCAGCTT CAGGCAGGCG 1300

CTGCTCGCCT ACCGCCAGCA CAATGGATCT CGAGGGATCT TCCATACCTA 1350

CCAGTTCTGC GCCTGCAGGT CGCGGCCGCA CTACTCTTTG ATGTATTACT 1400

CATATTACCA AGGAATAACT GGCGGGCACA GGGTCAGGTG CTGAAGGGAC 1450

ATTGTGAGAA GTGACCTAGA AGGCAAGAGG TGAGCCCTCT GTCACGCTGG 1500

CATAAGGGCC GCTTGAGGGC TCTTTGGTCA AGCAGTAACG CCAGTGTCTG 1550

GGAAGGCACC TGTTACTCAG CAGACCATGA AAGGGCGTCT CCCTTTCCTT 1600

GGAGCAGTCA GGGAACACTC TGCTCCACCA GCTTCTTGTG GGAGCCTGGA 1650

TATTATCCAG GCCTGCCCGC AGTCATCCGG AGGCCTAACC CCTCCCTGTG 1700

GTGCTTCAGT GGTCACACTC CTTGTCCACT TTCATGCTCC TCTTGGCCTC 1750

CTGGTTCCTC TTGGAAGTTT GTAGTAGATA GCAGAAGAAA TAGCGAAAGT 1800

CTTAAAGTCT TTGATCTTTC TTATAAGTGC AGAGAAGAAA TGCTGACGTA 1850

TGCTGCCTTC TCTCTCTCTG CTTCAGCTAC CTGAAGCCGC TTTCTTGTCT 1900

ATACCTGCTC TCTATCTGCT CACACTCCTC CGAGGCCAGC ACCATCCCAC 1950

TGTCTGTCTG GTTGTCCACA GAGCCTTTGT AGGTCGTTGG GGTCATGGGG 2000

AATTCCTCAA ATGTCTTCAT CCTGGAGGAA CCACGGGTCT CAGCCCCTCT 2050

GGCCAGGCAC CCGGGAAAGG ACACCCAGTT GTAATACCTG GCGGCCAGGC 2100

TGTGGCGCTG CAGGCTTGGC GGGCTGTCCT CAGCGTCAGC CTGGGCGATG 2150

TGTAGGGCCA TGGTGGACAC CTGCGAGAAG CTGCCCTCTT CTGAGCTCTG 2200

AGAGCTGCGC GGGGCCATGC AGACCTCCTC TTCCTCTTGC AGGCCCCTGC 2250

CCTGGAGCAG GTCCCCCAGG ATCTCCACCA GCTCCGAGAA TGCAGGTCTC 2300

GCCTTGGGGT CTCCGGACCA GCAGTTCAGC ATGATGCGGC GTATGGCGGG 2350

AGTGGCCAGC TCCGGGGCCC TCATCCTTGT GCCGTCTCTC AGCCGCTGGC 2400

AGAACTCCTC ATTGATCTGC ACCCCAGGGT ACGGGGAGGC CCCCAGAGAG 2450

AAGATCTCCC AGAGAAGCAC CCCAAAGGAC CACACGTCAC TCTGCGTGGT 2500

GTACACCTTG TCGAAGATGC TTTCAGGGGC CATCCACTTC AGGGGCAGCC 2550

GGGCACTGCC CTTGCGGACG TAGTCGGGGT CTTTGTAGAT GTCCCGGGCA 2600

AGGCCAAAGT CACAGATCTT CACCACGTCG CTTTCCGACA GCAGAATGTT 2650

CCGAGCAGCC AGGTCTCTGT GGATGCACTT TCGGGAAGCC AGGAACTCCA 2700

TCCCTCTGGC CACCTGGAAG CTGTAGCAGA CAAGATCTTC CATGGTCAGC 2750

GGGCTCAGCC ACAGGTCCTC AGCTTCTTGG TCTGGAGAAG CCCGCCTCGC 2800

TCCGCCCTCG GTCTTCGAGA ACCGCGCGAA GAGGACCCTG TCGCTGCTCC 2850

CCGGCCGCCT CCGATCCAGC CTGGCGAGCT CCACCATGGC GCGGAAGCGT 2900

CCGCGCTGCT CGGGAGACTT CTCCTGCGGA TGCACGAAGC TGGCTCGAGG 2950

GCGCCCAGTC GTCCGCCGCA GAGGCGCCTC CATTCCCCCG CCGCCCGCGG 3000

CGCCCCGCAG GCCGCCCGCT CACCGNGCAG GGGCTGCGGC CGCGACTCTA 3050

GAGTCGACCT GCAGAAGCTT GGCCGCCATG GCCCAACTTG TTTATTGCAG 3100

CTTATAATGG TTACAAATAA AGCAATAGCA TCACAAATTT CACAAATAAA 3150

GCATTTTTTT CACTGCATTC TAGTTGTGGT TTGTCCAAAC TCATCAATGT 3200

ATCTTATCAT GTCTGGATCG ATCGGGAATT AATTCGGCGC AGCACCATGG 3250

CCTGAAATAA CCTCTGAAAG AGGAACTTGG TTAGGTACCT TCTGAGGCGG 3300

AAAGAACCAG CTGTGGAATG TGTGTCAGTT AGGGTGTGGA AAGTCCCCAG 3350

GCTCCCCAGC AGGCAGAAGT ATGCAAAGCA TGCATCTCAA TTAGTCAGCA 3400

ACCAGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA GTATGCAAAG 3450

CATGCATCTC AATTAGTCAG CAACCATAGT CCCGCCCCTA ACTCCGCCCA 3500

TCCCGCCCCT AACTCCGCCC AGTTCCGCCC ATTCTCCGCC CCATGGCTGA 3550

CTAATTTTTT TTATTTATGC AGAGGCCGAG GCCGCCTCGG CCTCTGAGCT 3600

ATTCCAGAAG TAGTGAGGAG GCTTTTTTGG AGGCCTAGGC TTTTGCAAAA 3650

AGCTGTTAAC AGCTTGGCAC TGGCCGTCGT TTTACAACGT CGTGACTGGG 3700

AAAACCCTGG CGTTACCCAA CTTAATCGCC TTGCAGCACA TCCCCCCTTC 3750

GCCAGCTGGC GTAATAGCGA AGAGGCCCGC ACCGATCGCC CTTCCCAACA 3800

GTTGCGTAGC CTGAATGGCG AATGGCGCCT GATGCGGTAT TTTCTCCTTA 3850

CGCATCTGTG CGGTATTTCA CACCGCATAC GTCAAAGCAA CCATAGTACG 3900

CGCCCTGTAG CGGCGCATTA AGCGCGGCGG GTGTGGTGGT TACGCGCAGC 3950

GTGACCGCTA CACTTGCCAG CGCCCTAGCG CCCGCTCCTT TCGCTTTCTT 4000

CCCTTCCTTT CTCGCCACGT TCGCCGGCTT TCCCCGTCAA GCTCTAAATC 4050

GGGGGCTCCC TTTAGGGTTC CGATTTAGTG CTTTACGGCA CCTCGACCCC 4100

AAAAAACTTG ATTTGGGTGA TGGTTCACGT AGTGGGCCAT CGCCCTGATA 4150

GACGGTTTTT CGCCCTTTGA CGTTGGAGTC CACGTTCTTT AATAGTGGAC 4200

TCTTGTTCCA AACTGGAACA ACACTCAACC CTATCTCGGG CTATTCTTTT 4250

GATTTATAAG GGATTTTGCC GATTTCGGCC TATTGGTTAA AAAATGAGCT 4300

GATTTAACAA AAATTTAACG CGAATTTTAA CAAAATATTA ACGTTTACAA 4350

TTTTATGGTG CACTCTCAGT ACAATCTGCT CTGATGCCGC ATAGTTAAGC 4400

CAACTCCGCT ATCGCTACGT GACTGGGTCA TGGCTGCGCC CCGACACCCG 4450

CCAACACCCG CTGACGCGCC CTGACGGGCT TGTCTGCTCC CGGCATCCGC 4500

TTACAGACAA GCTGTGACCG TCTCCGGGAG CTGCATGTGT CAGAGGTTTT 4550

CACCGTCATC ACCGAAACGC GCGAGGCAGT ATTCTTGAAG ACGAAAGGGC 4600

CTCGTGATAC GCCTATTTTT ATAGGTTAAT GTCATGATAA TAATGGTTTC 4650

TTAGACGTCA GGTGGCACTT TTCGGGGAAA TGTGCGCGGA ACCCCTATTT 4700

GTTTATTTTT CTAAATACAT TCAAATATGT ATCCGCTCAT GAGACAATAA 4750

CCCTGATAAA TCTTCAATAA TATTGAAAAA GGAAGAGTAT GAGTATTCAA 4800

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TTTTTGCTCA CCCAGAAACG CTGGTGAAAG TAAAAGATGC TGAAGATCAG 4900

TTGGGTGCAC GAGTGGGTTA CATCGAACTG GATCTCAACA GCGGTAAGAT 4950

CCTTGAGAGT TTTCGCCCCG AAGAACGTTT TCCAATGATG AGCACTTTTA 5000

AAGTTCTGCT ATGTGGCGCG GTATTATCCC GTGATGACGC CGGGCAAGAG 5050

CAACTCGGTC GCCGCATACA CTATTCTCAG AATGACTTGG TTGAGTACTC 5100

ACCAGTCACA GAAAAGCATC TTACGGATGG CATGACAGTA AGAGAATTAT 5150

GCAGTGCTGC CATAACCATG AGTGATAACA CTGCGGCCAA CTTACTTCTG 5200

ACAACGATCG GAGGACCGAA GGAGCTAACC GCTTTTTTGC ACAACATGGG 5250

GGATCATGTA ACTCGCCTTG ATCGTTGGGA ACCGGAGCTG AATGAAGCCA 5300

TACCAAACGA CGAGCGTGAC ACCACGATGC CAGCAGCAAT GGCAACAACG 5350

TTGCGCAAAC TATTAACTGG CGAACTACTT ACTCTAGCTT CCCGGCAACA 5400

ATTAATAGAC TGGATGGAGG CGGATAAAGT TGCAGGACCA CTTCTGCGCT 5450

CGGCCCTTCC GGCTGGCTGG TTTATTGCTG ATAAATCTGG AGCCGGTGAG 5500

CGTGGGTCTC GCGGTATCAT TGCAGCACTG GGGCCAGATG GTAAGCCCTC 5550

CCGTATCGTA GTTATCTACA CGACGGGGAG TCAGGCAACT ATGGATGAAC 5600

GAAATAGACA GATCGCTGAG ATAGGTGCCT CACTGATTAA GCATTGGTAA 5650

CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA 5700

TTTTTAATTT AAAAGGATCT AGGTGAAGAT CCTTTTTGAT AATCTCATGA 5750

CCAAAATCCC TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA 5800

GAAAAGATCA AAGGATCTTC TTGAGATCCT TTTTTTCTGC GCGTAATCTG 5850

CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTTTGCCGG 5900

ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG 5950

CAGATACCAA ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCACTT 6000

CAAGAACTCT GTAGCACCGC CTACATACCT CGCTCTGCTA ATCCTGTTAC 6050

CAGTGGCTGC TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTCA 6100

AGACGATAGT TACCGGATAA GGCGCAGCGG TCGGGCTGAA CCGGGGGTTC 6150

GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC 6200

TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG GAGAAAGGCG 6250

GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA 6300

GCTTCCAGGG GGAAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC 6350

ACCTCTGACT TGAGCGTCGA TTTTTGTGAT GCTCGTCAGG GGGGCGGAGC 6400

CTATGGAAAA ACGCCAGCAA CGCGGCCTTT TTACGGTTCC TGGCCTTTTG 6450

CTGGCCTTTT GCTCACATGT TCTTTCCTGC GTTATCCCCT GATTCTGTGG 6500

ATAACCGTAT TACCGCCTTT GAGTGAGCTG ATACCGCTCG CCGCAGCCGA 6550

ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT 6600

ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCATTAA TCCAGCTGGC 6650

ACGACAGGTT TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAT 6700

GTGAGTTACC TCACTCATTA GGCACCCCAG GCTTTACACT TTATGCTTCC 6750

GGCTCGTATG TTGTGTGGAA TTGTGAGCGG ATAACAATTT CACACAGGAA 6800

ACAGCTATGA CCATGATTAC GAATTAA 6827

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 348 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe Arg Ala Met Val Glu
1 5 10 15

Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly Ser Ser Asp Arg Val
20 25 30

Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly Gly Ala Arg Arg Ala
35 40 45

Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp Leu Ser Pro Leu Thr
50 55 60

Met Glu Asp Leu Val Cys Tyr Ser Phe Gln Val Ala Arg Gly Met
65 70 75

Glu Phe Leu Ala Ser Arg Lys Cys Ile His Arg Asp Leu Ala Ala
80 85 90

Arg Asn Ile Leu Leu Ser Glu Ser Asp Val Val Lys Ile Cys Asp
95 100 105

Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp Pro Asp Tyr Val Arg
110 115 120

Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp Met Ala Pro Glu Ser
125 130 135

Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
140 145 150

Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser Pro Tyr
155 160 165

Pro Gly Val Gln Ile Asn Glu Glu Phe Cys Gln Arg Leu Arg Asp
170 175 180

Gly Thr Arg Met Arg Ala Pro Glu Leu Ala Thr Pro Ala Ile Arg
185 190 195

Arg Ile Met Leu Asn Cys Trp Ser Gly Asp Pro Lys Ala Arg Pro
200 205 210

Ala Phe Ser Glu Leu Val Glu Ile Leu Gly Asp Leu Leu Gln Gly
215 220 225

Arg Gly Leu Gln Glu Glu Glu Glu Val Cys Met Ala Pro Arg Ser
230 235 240

Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser Gln Val Ser Thr Met
245 250 255

Ala Leu His Ile Ala Gln Ala Asp Ala Glu Asp Ser Pro Pro Ser
260 265 270

Leu Gln Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn Trp Val Ser
275 280 285

Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly Ser Ser
290 295 300

Arg Met Lys Thr Phe Glu Glu Phe Pro Met Thr Pro Thr Thr Tyr
305 310 315

Lys Gly Ser Val Asp Asn Gln Thr Asp Ser Gly Met Val Leu Ala
320 325 330

Ser Glu Glu Cys Glu Gln Ile Glu Ser Arg Tyr Arg Gln Glu Ser
335 340 345

Gly Phe Arg
348

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7607 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACTTGGCT TCGTTAGAAC GCGGCTACAA TTAATACATA 800

ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA GAATAACATC 850

CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT 900

CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT 950

CGAGTCGACT TTTTTTTTTT TTTTTGTAGG CCAAAGGGTA CTTCTTTTTC 1000

TTTATTAATT ACTCAGAAGT CTAGGCCACA GCAATCTACT GTTCTCCTCT 1050

CATTTTCCTA AACTATTTTG ATACCTATTT CTCAGACTTT ATGGGCTATT 1100

AGACATTTCT CACATTTCCA TAGATAATAA CTCATCCGTT TTGCAACCTG 1150

ATTCTCAATA TTAAGAGATT AAAACTAATG TATATGACTC TCAGTTGACA 1200

CATACTGAAG TACAGAAAAA TTCCATCATT TCCTTCTGCA AAATGAAAAA 1250

GACTTCGTTT TCTCAACAGC TGCATCATTT TTTTATGCAT AGAAAAAAAT 1300

GTGCAATTAC TCCAAGTACA ATCAAGTCAT TTAACATGGC TTTACCATCA 1350

TTGTAGTTAC AGGATATTTT AAAAGAGAAA AAAAAATCTC AAAGCACAGG 1400

TCCTGCTGTG CAGCAAAGCA ATCAAATTCC TTCATAATAA CAGCCTGATG 1450

GGATTCAGCA ATCTGAGGAA TAATGAATAA CCACTCTAAT CAGTAAACAG 1500

GAAAATGCTA CAACAGTCAC TGAGTAAAAA TTGGACTATC ATCTGTTGAT 1550

TCTCTTGATC GACATTTCAA ACAATAAATG GAAATGTAAG TATCTCTTAA 1600

AAAGAAAAAT AACTTGGTTT AGTGTGCTTA ATTTTACCAG GCAGTGAGGA 1650

AATTATATAT CACCTTGACT GTCCTGCAGT GTTGCCCAGT CAATAAAATG 1700

CACAAATAAT CTTTTTCATA ATACATGGCC AACTTTATCC TATCACTTGA 1750

ATATGTCAGG ATAAACTGAT TGTGCAGTTG GTTGATAACA TTGTATTTTG 1800

GAATGGATTA TTTGAATTTG TTTTGCTACT TTATTATTTG ATATTCTTCT 1850

CCAGTGTTCA TCTTATGAAG TTATTTGCAT CTGAATATGA AGAGTCTGTT 1900

TCAAAATAGT CTTCAAGTTT CCAACGCAGT GTCTCAAATG TAGGTCGTTC 1950

CTTAGGCTCT GCATTCCAGC ACTCCAACAT GATGTTGTAA AATTGCTGTG 2000

GACAGTTGGA TGGTTGCGGA AGTCTATAGT TTTGAGCCAA CATCTGGATT 2050

ACCTGGGCAC CTGTCATACC ACTGTAAGGC ATTTTGCCAT AAGTAATGAT 2100

TTCATAAAGA AGGATTCCAA ATGACCATAC ATCGGACTTA ATGCTGAATT 2150

TATTACTACG AATGGCTTCG GGCGCAGTCC ACTTCACCGG CAGCTTTATT 2200

TCGTGTCTAG ATTCATAGAT GTCTTCATTA TCTACCTTAA AAACTCTGGC 2250

AAGTCCAAAA TCTGCTACTT TGTAGATATT ATGTTCACCA ACGAGGACAT 2300

TTCTGGCAGC CAGATCTCTG TGAATGTAGT TCCGAGACTC CAGATAGGCC 2350

ATTCCAGAGG CAACCTGTGC CGCCATGTCT ACCTGTTGAG TCAGATGGAT 2400

TTTTGATCCA GTGTCATTTT GGAGATATTC TTGCAGACTT CCATGTCTCA 2450

TCAACTCTGT AATAATATAA ATTGGATCTT CTAAAGTGCA AACAGCATAA 2500

AGCTGGATAA GCTTTGGATG TCTTAGGTTC TTCATTATCT GTGCCTCCCT 2550

CAGGAAGTCA TTTGGATCCA TTGAACCTGG TTTTAATGTT TTCACTGCTA 2600

CTGGAGTGGT ATTGTTCCAC AGACCTTCCC ATACTTCGCC AAACTGACCA 2650

GATCCCAATC GCTTCAGAAG CTGTATGGAG TTGCGGTCTA TCTCCCATTG 2700

GTCCACGGTT TTATACGACA AATCAAATGG AGCTGGGACC TGGATCTTTA 2750

AGCATGGTTT CCCCAGCTTG ACACACAGGC CGTCACTTGT CTTGGTGTAG 2800

TGGCTCACAA ATTCGTTCAG TGTTGAAAAG ATTCTTCTTC GCGTGAGAAA 2850

AAATCCCCCT TCATCCAGTC TTTTAATTCT GTAGTGTTTT ACAACTGCTC 2900

CATCTAAAAC TGAAAGAGAG AATTCTCCTT TTTGGCTTTC ACTTTCTCTG 2950

ATTAGAAAGG AACCGGTCTT GTTTTCTGAA TATAATAGTT GTTTCTCTGC 3000

ATCTGATCTT CCGATTGCTC CAAAGAACCA CGGCTCTGCC TGTAGGCTTC 3050

TGTCCTCAGC CACGTAGTTA GAAGGAATAT AGCCTTGTAG TTGCTGACTG 3100

GAGCCATCTC GTCTTTTCTC CAAGTGTCTG GCAAACCACC AGCCCTCATG 3150

CAAAGTGTCC AGAACTTGAA GTTTGTCACC TGCTCGGAAG CTCAAGTCCT 3200

CAGCAGTCCG AGCCTGGTAA TCAAACAAAG CCACAAAGTA GTGGCCATGC 3250

CTCTGTGACT GGGGAGAGCA AAGGGCCCCT GGATTTTCAA TCACGGTTGA 3300

CTTGTCTGCC TCCGTGGACA AACAGGGGAG ATAGGGTTCT AGGTACTCCC 3350

AGAGCCTCTG ACAGATGTTG CTCATTGTGC CTTGGTGGGG AGAAGAGGAG 3400

CAGGGCTTCT CCCTCTCCCC TTAGTCTCTG CGATCCACCT TATCTTCCTT 3450

CACCAGGCAA CTTTGAAGTC AGCACCAACT CACCATACTT CGGAGAGTAT 3500

GCAAAGTCCC GTTTCAGATC AGTCCAGCAG CTGGGTTGCA GCAAGTCCTA 3550

CCTGGAGAGA CTTACCGGCT TGCTTTCTGT GGCTGGAGGT GCTACCCCGA 3600

GGCAAAACTG AGCAGGAGCT GGGCAGCTGC TCACTAGGAA GGTGTCTTTT 3650

CTTCTTATCT GCTTAAGAAT CCCACAACAA AAATAAAATA AAATTAAAAG 3700

GGCTTTATTT AGACAAATAT CTGAGAACAG AATGGTGCCA TCTTGCCTTT 3750

TGTCCCAATA AAAAGTTAGC AAGAGGAAGC TACTAACCCC TGGTAAAACC 3800

TCCACGTCTT GCTTTCGCCA GGGTCGACTC GAGGGATCTT CCATACCTAC 3850

CAGTTCTGCG CCTGCAGGTC GCGGCCGCGA CTCTAGAGTC GACCTGCAGA 3900

AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA 3950

AATAAAGCAA TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG 4000

CATTCTAGTT GTGGTTTGTC CAAACTCATC AATGTATCTT ATCATGTCTG 4050

GATCGGGAAT TAATTCGGCG CAGCACCATG GCCTGAAATA ACCTCTGAAA 4100

GAGGAACTTG GTTAGGTACC TTCTGAGGCG GAAAGAACCA GCTGTGGAAT 4150

GTGTGTCAGT TAGGGTGTGG AAAGTCCCCA GGCTCCCCAG CAGGCAGAAG 4200

TATGCAAAGC ATGCATCTCA ATTAGTCAGC AACCAGGTGT GGAAAGTCCC 4250

CAGGCTCCCC AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA 4300

GCAACCATAG TCCCGCCCCT AACTCCGCCC ATCCCGCCCC TAACTCCGCC 4350

CAGTTCCGCC CATTCTCCGC CCCATGGCTG ACTAATTTTT TTTATTTATG 4400

CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC TATTCCAGAA GTAGTGAGGA 4450

GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA AAGCTGTTAA CAGCTTGGCA 4500

CTGGCCGTCG TTTTACAACG TCGTGACTGG GAAAACCCTG GCGTTACCCA 4550

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ACACCGCATA CGTCAAAGCA ACCATAGTAC GCGCCCTGTA GCGGCGCATT 4750

AAGCGCGGCG GGTGTGGTGG TTACGCGCAG CGTGACCGCT ACACTTGCCA 4800

GCGCCCTAGC GCCCGCTCCT TTCGCTTTCT TCCCTTCCTT TCTCGCCACG 4850

TTCGCCGGCT TTCCCCGTCA AGCTCTAAAT CGGGGGCTCC CTTTAGGGTT 4900

CCGATTTAGT GCTTTACGGC ACCTCGACCC CAAAAAACTT GATTTGGGTG 4950

ATGGTTCACG TAGTGGGCCA TCGCCCTGAT AGACGGTTTT TCGCCCTTTG 5000

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AACACTCAAC CCTATCTCGG GCTATTCTTT TGATTTATAA GGGATTTTGC 5100

CGATTTCGGC CTATTGGTTA AAAAATGAGC TGATTTAACA AAAATTTAAC 5150

GCGAATTTTA ACAAAATATT AACGTTTACA ATTTTATGGT GCACTCTCAG 5200

TACAATCTGC TCTGATGCCG CATAGTTAAG CCAGCCCCGA CACCCGCCAA 5250

CACCCGCTGA CGCGCCCTGA CGGGCTTGTC TGCTCCCGGC ATCCGCTTAC 5300

AGACAAGCTG TGACCGTCTC CGGGAGCTGC ATGTGTCAGA GGTTTTCACC 5350

GTCATCACCG AAACGCGCGA GACGAAAGGG CCTCGTGATA CGCCTATTTT 5400

TATAGGTTAA TGTCATGATA ATAATGGTTT CTTAGACGTC AGGTGGCACT 5450

TTTCGGGGAA ATGTGCGCGG AACCCCTATT TGTTTATTTT TCTAAATACA 5500

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AATATTGAAA AAGGAAGAGT ATGAGTATTC AACATTTCCG TGTCGCCCTT 5600

ATTCCCTTTT TTGCGGCATT TTGCCTTCCT GTTTTTGCTC ACCCAGAAAC 5650

GCTGGTGAAA GTAAAAGATG CTGAAGATCA GTTGGGTGCA CGAGTGGGTT 5700

ACATCGAACT GGATCTCAAC AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC 5750

GAAGAACGTT TTCCAATGAT GAGCACTTTT AAAGTTCTGC TATGTGGCGC 5800

GGTATTATCC CGTATTGACG CCGGGCAAGA GCAACTCGGT CGCCGCATAC 5850

ACTATTCTCA GAATGACTTG GTTGAGTACT CACCAGTCAC AGAAAAGCAT 5900

CTTACGGATG GCATGACAGT AAGAGAATTA TGCAGTGCTG CCATAACCAT 5950

GAGTGATAAC ACTGCGGCCA ACTTACTTCT GACAACGATC GGAGGACCGA 6000

AGGAGCTAAC CGCTTTTTTG CACAACATGG GGGATCATGT AACTCGCCTT 6050

GATCGTTGGG AACCGGAGCT GAATGAAGCC ATACCAAACG ACGAGCGTGA 6100

CACCACGATG CCTGTAGCAA TGGCAACAAC GTTGCGCAAA CTATTAACTG 6150

GCGAACTACT TACTCTAGCT TCCCGGCAAC AATTAATAGA CTGGATGGAG 6200

GCGGATAAAG TTGCAGGACC ACTTCTGCGC TCGGCCCTTC CGGCTGGCTG 6250

GTTTATTGCT GATAAATCTG GAGCCGGTGA GCGTGGGTCT CGCGGTATCA 6300

TTGCAGCACT GGGGCCAGAT GGTAAGCCCT CCCGTATCGT AGTTATCTAC 6350

ACGACGGGGA GTCAGGCAAC TATGGATGAA CGAAATAGAC AGATCGCTGA 6400

GATAGGTGCC TCACTGATTA AGCATTGGTA ACTGTCAGAC CAAGTTTACT 6450

CATATATACT TTAGATTGAT TTAAAACTTC ATTTTTAATT TAAAAGGATC 6500

TAGGTGAAGA TCCTTTTTGA TAATCTCATG ACCAAAATCC CTTAACGTGA 6550

GTTTTCGTTC CACTGAGCGT CAGACCCCGT AGAAAAGATC AAAGGATCTT 6600

CTTGAGATCC TTTTTTTCTG CGCGTAATCT GCTGCTTGCA AACAAAAAAA 6650

CCACCGCTAC CAGCGGTGGT TTGTTTGCCG GATCAAGAGC TACCAACTCT 6700

TTTTCCGAAG GTAACTGGCT TCAGCAGAGC GCAGATACCA AATACTGTTC 6750

TTCTAGTGTA GCCGTAGTTA GGCCACCACT TCAAGAACTC TGTAGCACCG 6800

CCTACATACC TCGCTCTGCT AATCCTGTTA CCAGTGGCTG CTGCCAGTGG 6850

CGATAAGTCG TGTCTTACCG GGTTGGACTC AAGACGATAG TTACCGGATA 6900

AGGCGCAGCG GTCGGGCTGA ACGGGGGGTT CGTGCACACA GCCCAGCTTG 6950

GAGCGAACGA CCTACACCGA ACTGAGATAC CTACAGCGTG AGCTATGAGA 7000

AAGCGCCACG CTTCCCGAAG GGAGAAAGGC GGACAGGTAT CCGGTAAGCG 7050

GCAGGGTCGG AACAGGAGAG CGCACGAGGG AGCTTCCAGG GGGAAACGCC 7100

TGGTATCTTT ATAGTCCTGT CGGGTTTCGC CACCTCTGAC TTGAGCGTCG 7150

ATTTTTGTGA TGCTCGTCAG GGGGGCGGAG CCTATGGAAA AACGCCAGCA 7200

ACGCGGCCTT TTTACGGTTC CTGGCCTTTT GCTGGCCTTT TGCTCACATG 7250

TTCTTTCCTG CGTTATCCCC TGATTCTGTG GATAACCGTA TTACCGCCTT 7300

TGAGTGAGCT GATACCGCTC GCCGCAGCCG AACGACCGAG CGCAGCGAGT 7350

CAGTGAGCGA GGAAGCGGAA GAGCGCCCAA TACGCAAACC GCCTCTCCCC 7400

GCGCGTTGGC CGATTCATTA ATGCAGCTGG CACGACAGGT TTCCCGACTG 7450

GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG CTCACTCATT 7500

AGGCACCCCA GGCTTTACAC TTTATGCTTC CGGCTCGTAT GTTGTGTGGA 7550

ATTGTGAGCG GATAACAATT TCACACAGGA AACAGCTATG ACATGATTAC 7600

GAATTAA 7607

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 505 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Ser Asn Ile Cys Gln Arg Leu Trp Glu Tyr Leu Glu Pro Tyr
1 5 10 15

Leu Pro Cys Leu Ser Thr Glu Ala Asp Lys Ser Thr Val Ile Glu
20 25 30

Asn Pro Gly Ala Leu Cys Ser Pro Gln Ser Gln Arg His Gly His
35 40 45

Tyr Phe Val Ala Leu Phe Asp Tyr Gln Ala Arg Thr Ala Glu Asp
50 55 60

Leu Ser Phe Arg Ala Gly Asp Lys Leu Gln Val Leu Asp Thr Leu
65 70 75

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His Glu Gly Trp Trp Phe Ala Arg His Leu Glu Lys Arg Arg Asp
                  80                  85                  90

Gly Ser Ser Gln Gln Leu Gln Gly Tyr Ile Pro Ser Asn Tyr Val
                  95                 100                 105

Ala Glu Asp Arg Ser Leu Gln Ala Glu Pro Trp Phe Phe Gly Ala
                 110                 115                 120

Ile Gly Arg Ser Asp Ala Glu Lys Gln Leu Leu Tyr Ser Glu Asn
                 125                 130                 135

Lys Thr Gly Ser Phe Leu Ile Arg Glu Ser Glu Ser Gln Lys Gly
                 140                 145                 150

Glu Phe Ser Leu Ser Val Leu Asp Gly Ala Val Val Lys His Tyr
                 155                 160                 165

Arg Ile Lys Arg Leu Asp Glu Gly Gly Phe Phe Leu Thr Arg Arg
                 170                 175                 180

Arg Ile Phe Ser Thr Leu Asn Glu Phe Val Ser His Tyr Thr Lys
                 185                 190                 195

Thr Ser Asp Gly Leu Cys Val Lys Leu Gly Lys Pro Cys Leu Lys
                 200                 205                 210

Ile Gln Val Pro Ala Pro Phe Asp Leu Ser Tyr Lys Thr Val Asp
                 215                 220                 225

Gln Trp Glu Ile Asp Arg Asn Ser Ile Gln Leu Leu Lys Arg Leu
                 230                 235                 240

Gly Ser Gly Gln Phe Gly Glu Val Trp Glu Gly Leu Trp Asn Asn
                 245                 250                 255

Thr Thr Pro Val Ala Val Lys Thr Leu Lys Pro Gly Ser Met Asp
                 260                 265                 270

Pro Asn Asp Phe Leu Arg Glu Ala Gln Ile Met Lys Asn Leu Arg
                 275                 280                 285

His Pro Lys Leu Ile Gln Leu Tyr Ala Val Cys Thr Leu Glu Asp
                 290                 295                 300

Pro Ile Tyr Ile Ile Thr Glu Leu Met Arg His Gly Ser Leu Gln
                 305                 310                 315

Glu Tyr Leu Gln Asn Asp Thr Gly Ser Lys Ile His Leu Thr Gln
                 320                 325                 330

Gln Val Asp Met Ala Ala Gln Val Ala Ser Gly Met Ala Tyr Leu
                 335                 340                 345

Glu Ser Arg Asn Tyr Ile His Arg Asp Leu Ala Ala Arg Asn Val
                 350                 355                 360
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Leu Val Gly Glu His Asn Ile Tyr Lys Val Ala Asp Phe Gly Leu
365 370 375

Ala Arg Val Phe Lys Val Asp Asn Glu Asp Ile Tyr Glu Ser Arg
380 385 390

His Glu Ile Lys Leu Pro Val Lys Trp Thr Ala Pro Glu Ala Ile
395 400 405

Arg Ser Asn Lys Phe Ser Ile Lys Ser Asp Val Trp Ser Phe Gly
410 415 420

Ile Leu Leu Tyr Glu Ile Ile Thr Tyr Gly Lys Met Pro Tyr Ser
425 430 435

Gly Met Thr Gly Ala Gln Val Ile Gln Met Leu Ala Gln Asn Tyr
440 445 450

Arg Leu Pro Gln Pro Ser Asn Cys Pro Gln Gln Phe Tyr Asn Ile
455 460 465

Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe
470 475 480

Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser
485 490 495

Ser Tyr Ser Asp Ala Asn Asn Phe Ile Arg
500 505

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 404 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GCGGCCGCAG AGAAAGCAGA GGATGGGGCT TAGCAGCTGG CAGAGCCAGG 50

AGCGGGGAGG TAGCAGAAAG ACCACAAGTA CAAAGAAGTC CTGAAACTTT 100

GGTTTTGCTG CTGCAGCCCA TTGAGAGTGA CGACATGGAG CACAAGACCC 150

TGAAGATCAC CGACTTTGGC CTGGCCCGAG AGTGGCACAA AACCACACAA 200

ATGAGTGCCG CNGGCACCTA CNCCTGGATG GCTCCTGAGG TTATCAAGGC 250

CTCCACCTTC TCTAAGGGCA GTGACGTCTG GAGTTTTGGG GTGCTGCTGT 300

GGGAACTGCT GACCGGGGAG NTGCCATACC GTGGCATTGA CTGCCTTGCT 350

GTGGCCTATG GCGTAGCTGT TAACAAGCTC ACACTGCCAT CCATCCACCT 400

GGCC 404

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3120 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

ATGAGAGCGT TGGCGCGCGA CGGCGGCCAG CTGCCGCTGC TCGTTGTTTT 50

TTCTGCAATG ATATTTGGGA CTATTACAAA TCAAGATCTG CCTGTGATCA 100

AGTGTGTTTT AATCAATCAT AAGAACAATG ATTCATCAGT GGGGAAGTCA 150

TCATCATATC CCATGGTATC AGAATCCCCG GAAGACCTCG GGTGTGCGTT 200

GAGACCCCAG AGCTCAGGGA CAGTGTACGA AGCTGCCGCT GTGGAAGTGG 250

ATGTATCTGC TTCCATCACA CTGCAAGTGC TGGTCGATGC CCCAGGGAAC 300

ATTTCCTGTC TCTGGGTCTT TAAGCACAGC TCCCTGAATT GCCAGCCACA 350

TTTTGATTTA CAAAACAGAG GAGTTGTTTC CATGGTCATT TTGAAAATGA 400

CAGAAACCCA AGCTGGAGAA TACCTACTTT TTATTCAGAG TGAAGCTACC 450

AATTACACAA TATTGTTTAC AGTGAGTATA AGAAATACCC TGCTTTACAC 500

ATTAAGAAGA CCTTACTTTA GAAAAATGGA AAACCAGGAC GCCCTGGTCT 550

GCATATCTGA GAGCGTTCCA GAGCGGATCC TGGAATGGGT GCTTTGCGAT 600

TCACAGGGGG AAAGCTGTAA AGAAGAAAGT CCAGCTGTTG TTAAAAAGGA 650

GGAAAAAGTG CTTCATGAAT TATTTGGGAC GGACATAAGG TGCTGTGCCA 700

GAAATGAACT GGGCAGGGAA TGCACCAGGC TGTTCACAAT AGATCTAAAT 750

CAAACTCCTC AGACCACATT GCCACAATTA TTTCTTAAAG TAGGGGAACC 800

CTTATGGATA AGGTGCAAAG CTGTTCATGT GAACCATGGA TTCGGGCTCA 850

CCTGGGAATT AGAAAACAAA GCACTCGAGG AGGGCAACTA CTTTGAGATG 900

AGTACCTATT CAACAAACAG AACTATGATA CGGATTCTGT TTGCTTTTGT 950

ATCATCAGTG GCAAGAAACG ACACCGGATA CTACACTTGT TCCTCTTCAA 1000

AGCATCCCAG TCAATCAGCT TTGGTTACCA TCGTAGAAAA GGGATTTATA 1050

AATGCTACCA ATTCAAGTGA AGATTATGAA ATTGACCAAT ATGAAGAGTT 1100

TTGTTTTTCT GTCAGGTTTA AAGCCTACCC ACAAATCAGA TGTACGTGGA 1150

CCTTCTCTCG AAAATCATTT CCTTGTGAGC AAAAGGGTCT TGATAACGGA 1200

TACAGCATAT CCAAGTTTTG CAATCATAAG CACCAGCCAG GAGAATATAT 1250

ATTCCATGCA GAAAATGATG ATGCCCAATT TACCAAAATG TTCACGCTGT 1300

ATATAAGAAG GAAACCTCAA GTCCTCGCAG AAGCTTCGGC AAGTCAGGCG 1350

TCCTGTTTCT CGGATGGATA CCCATTACCA TCTTGGACCT GGAAGAAGTG 1400

TTCAGACAAG TCTCCCAACT GCACAGAAGA GATCACAGAA GGAGTCTGGA 1450

ATAGAAAGGC TAACAGAAAA GTGTTTGGAC AGTGGGTGTC GAGCAGTACT 1500

CTAAACATGA GTGAAGCCAT AAAAGGGTTC CTGGTCAAGT GCTGTGCATA 1550

CAATTCCCTT GGCACATCTT GTGAGACGAT CCTTTTAAAC TCTCCAGGCC 1600

CCTTCCCTTT CATCCAAGAC AACATCTCAT TCTATGCAAC AATTGGTGTT 1650

TGTCTCCTCT TCATTGTCGT TTTAACCCTG CTAATTTGTC ACAAGTACAA 1700

AAAGCAATTT AGGTATGAAA GCCAGCTACA GATGGTACAG GTGACCGGAT 1750

CCTCAGATTA TGAGTACTTC TACGTTGATT TCAGAGAATA TGAATATGAT 1800

GTCAAATGGG AGTTTCCAAG AGAAAATTTA GAGTTTGGGA AGGTACTAGG 1850

ATCAGGTGCT TTTGGAAAAG TGATGAACGC AACAGCTTAT GGAATTAGCA 1900

AAACAGGAGT CTCAATCCAG GTTACCGTCA AAATGCTGAA AGAAAAAGCA 1950

GACAGCTCTG AAAGAGAGGC ACTCATGTCA GAACTCAAGA TGATGACCCA 2000

GCTGGGAAGC CACGAGAATA TTGTGAACCT GCTGGGGGCG TGCACACTGT 2050

CAGGACCAAT TTACTTGATT TTTGAATACT GTTGCTATGG TGATCTTCTC 2100

AACTATCTAA GAAGTAAAAG AGAAAAATTT CACAGGACTT GGACAGAGAT 2150

TTTCAAGGAA CACAATTTCA GTTTTTACCC CACTTTCCAA TCACATCCAA 2200

ATTCCAGCAT GCCTGGTTCA AGAGAAGTTC AGATACACCC GGACTCGGAT 2250

CAAATCTCAG GGCTTCATGG GAATTCATTT CACTCTGAAG ATGAAATTGA 2300

ATATGAAAAC CAAAAAAGGC TGGAAGAAGA GGAGGACTTG AATGTGCTTA 2350

CATTTGAAGA TCTTCTTTGC TTTGCATATC AAGTTGCCAA AGGAATGGAA 2400

TTTCTGGAAT TTAAGTCGTG TGTTCACAGA GACCTGGCCG CCAGGAACGT 2450

GCTTGTCACC CACGGGAAAG TGGTGAAGAT ATGTGACTTT GGATTGGCTC 2500

GAGATATCAT GAGTGATTCC AACTATGTTG TCAGGGGCAA TGCCCGTCTG 2550

CCTGTAAAAT GGATGGCCCC CGAAAGCCTG TTTGAAGGCA TCTACACCAT 2600

TAAGAGTGAT GTCTGGTCAT ATGGAATATT ACTGTGGGAA ATCTTCTCAC 2650

TTGGTGTGAA TCCTTACCCT GGCATTCCGG TTGATGCTAA CTTCTACAAA 2700

CTGATTCAAA ATGGATTTAA AATGGATCAG CCATTTTATG CTACAGAAGA 2750

AATATACATT ATAATGCAAT CCTGCTGGGC TTTTGACTCA AGGAAACGGC 2800

CATCCTTCCC TAATTTGACT TCGTTTTTAG GATGTCAGCT GGCAGATGCA 2850

GAAGAAGCGA TGTATCAGAA TGTGGATGGC CGTGTTTCGG AATGTCCTCA 2900

CACCTACCAA AACAGGCGAC CTTTCAGCAG AGAGATGGAT TTGGGGCTAC 2950

TCTCTCCGCA GGCTCAGGTC GAAGATTCGT AGAGGAACAA TTTAGTTTTA 3000

AGGACTTCAT CCCTCCACCT ATCCCTAACA GGCTGTAGAT TACCAAAACA 3050

AGGTTAATTT CATCACTAAA AGAAAATCTA TTATCAACTG CTGCTTCACC 3100

AGACTTTTCT CTAGAGAGCG 3120

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3969 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCGGCGTCCA CCCGCCCAGG GAGAGTCAGA CCTGGGGGGG CGAGGGCCCC 50

CCAAACTCAG TTCGGATCCT ACCCGAGTGA GGCGGCGCCA TGGAGCTCCG 100

GGTGCTGCTC TGCTGGGCTT CGTTGGCCGC AGCTTTGGAA GAGACCCTGC 150

TGAACACAAA ATTGGAAACT GCTGATCTGA AGTGGGTGAC ATTCCCTCAG 200

GTGGACGGGC AGTGGGAGGA ACTGAGCGGC CTGGATGAGG AACAGCACAG 250

CGTGCGCACC TACGAAGTGT GTGACGTGCA GCGTGCCCCG GGCCAGGCCC 300

ACTGGCTTCG CACAGGTTGG GTCCCACGGC GGGGCGCCGT CCACGTGTAC 350

GCCACGCTGC GCTTCACCAT GCTCGAGTGC CTGTCCCTGC CTCGGGCTGG 400

GCGCTCCTGC AAGGAGACCT TCACCGTCTT CTACTATGAG AGCGATGCGG 450

ACACGGCCAC GGCCCTCACG CCAGCCTGGA TGGAGAACCC CTACATCAAG 500

GTGGACACGG TGGCCGCGGA GCATCTCACC CGGAAGCGCC CTGGGGCCGA 550

GGCCACCGGG AAGGTGAATG TCAAGACGCT GCGTCTGGGA CCGCTCAGCA 600

AGGCTGGCTT CTACCTGGCC TTCCAGGACC AGGGTGCCTG CATGGCCCTG 650

CTATCCCTGC ACCTCTTCTA CAAAAAGTGC GCCCAGCTGA CTGTGAACCT 700

GACTCGATTC CCGGAGACTG TGCCTCGGGA GCTGGTTGTG CCCGTGGCCG 750

GTAGCTGCGT GGTGGATGCC GTCCCCGCCC CTGGCCCCAG CCCCAGCCTC 800

TACTGCCGTG AGGATGGCCA GTGGGCCGAA CAGCCGGTCA CGGGCTGCAG 850

CTGTGCTCCG GGGTTCGAGG CAGCTGAGGG GAACACCAAG TGCCGAGCCT 900

GTGCCCAGGG CACCTTCAAG CCCCTGTCAG GAGAAGGGTC CTGCCAGCCA 950

TGCCCAGCCA ATAGCCACTC TAACACCATT GGATCAGCCG TCTGCCAGTG 1000

CCGCGTCGGG TACTTCCGGG CACGCACAGA CCCCCGGGGT GCACCCTGCA 1050

CCACCCCTCC TTCGGCTCCG CGGAGCGTGG TTTCCCGCCT GAACGGCTCC 1100

TCCCTGCACC TGGAATGGAG TGCCCCCCTG GAGTCTGGTG GCCGAGAGGA 1150

CCTCACCTAC GCCCTCCGCT GCCGGGAGTG CCGACCCGGA GGCTCCTGTG 1200

CGCCCTGCGG GGGAGACCTG ACTTTTGACC CCGGCCCCCG GGACCTGGTG 1250

GAGCCCTGGG TGGTGGTTCG AGGGCTACGT CCTGACTTCA CCTATACCTT 1300

TGAGGTCACT GCATTGAACG GGGTATCCTC CTTAGCCACG GGGCCCGTCC 1350

CATTTGAGCC TGTCAATGTC ACCACTGACC GAGAGGTACC TCCTGCAGTG 1400

TCTGACATCC GGGTGACGCG GTCCTCACCC AGCAGCTTGA GCCTGGCCTG 1450

GGCTGTTCCC CGGGCACCCA GTGGGGCTGT GCTGGACTAC GAGGTCAAAT 1500

ACCATGAGAA GGGCGCCGAG GGTCCCAGCA GCGTGCGGTT CCTGAAGACG 1550

TCAGAAAACC GGGCAGAGCT GCGGGGGCTG AAGCGGGGAG CCAGCTACCT 1600

GGTGCAGGTA CGGGCGCGCT CTGAGGCCGG CTACGGGCCC TTCGGCCAGG 1650

AACATCACAG CCAGACCCAA CTGGATGAGA GCGAGGGCTG GCGGGAGCAG 1700

CTGGCCCTGA TTGCGGGCAC GGCAGTCGTG GGTGTGGTCC TGGTCCTGGT 1750

GGTCATTGTG GTCGCAGTTC TCTGCCTCAG GAAGCAGAGC AATGGGAGAG 1800

AAGCAGAATA TTCGGACAAA CACGGACAGT ATCTCATCGG ACATGGTACT 1850

AAGGTCTACA TCGACCCCTT CACTTATGAA GACCCTAATG AGGCTGTGAG 1900

GGAATTTGCA AAAGAGATCG ATGTCTCCTA CGTCAAGATT GAAGAGGTGA 1950

TTGGTGCAGG TGAGTTTGGC GAGGTGTGCC GGGGGCGGCT CAAGGCCCCA 2000

GGGAAGAAGG AGAGCTGTGT GGCAATCAAG ACCCTGAAGG GTGGCTACAC 2050

GGAGCGGCAG CGGCGTGAGT TTCTGAGCGA GGCCTCCATC ATGGGCCAGT 2100

TCGAGCACCC CAATATCATC CGCCTGGAGG GCGTGGTCAC CAACAGCATG 2150

CCCGTCATGA TTCTCACAGA GTTCATGGAG AACGGCGCCC TGGACTCCTT 2200

CCTGCGGCTA AACGACGGAC AGTTCACAGT CATCCAGCTC GTGGGCATGC 2250

TGCGGGGCAT CGCCTCGGGC ATGCGGTACC TTGCCGAGAT GAGCTACGTC 2300

CACCGAGACC TGGCTGCTCG CAACATCCTA GTCAACAGCA ACCTCGTCTG 2350

CAAAGTGTCT GACTTTGGCC TTTCCCGATT CCTGGAGGAG AACTCTTCCG 2400

ATCCCACCTA CACGAGCTCC CTGGGAGGAA AGATTCCCAT CCGATGGACT 2450

GCCCCGGAGG CCATTGCCTT CCGGAAGTTC ACTTCCGCCA GTGATGCCTG 2500

GAGTTACGGG ATTGTGATGT GGGAGGTGAT GTCATTTGGG GAGAGGCCGT 2550

ACTGGGACAT GAGCAATCAG GACGTGATCA ATGCCATTGA ACAGGACTAC 2600

CGGCTGCCCC CGCCCCCAGA CTGTCCCACC TCCCTCCACC AGCTCATGCT 2650

GGACTGTTGG CAGAAAGACC GGAATGCCCG GCCCCGCTTC CCCCAGGTGG 2700

TCAGCGCCCT GGACAAGATG ATCCGGAACC CCGCCAGCCT CAAAATCGTG 2750

GCCCGGGAGA ATGGCGGGGC CTCACACCCT CTCCTGGACC AGCGGCAGCC 2800

TCACTACTCA GCTTTTGGCT CTGTGGGCGA GTGGCTTCGG GCCATCAAAA 2850

TGGGAAGATA CGAAGAAAGT TTCGCAGCCG CTGGCTTTGG CTCCTTCGAG 2900

CTGGTCAGCC AGATCTCTGC TGAGGACCTG CTCCGAATCG GAGTCACTCT 2950

GGCGGGACAC CAGAAGAAAA TCTTGGCCAG TGTCCAGCAC ATGAAGTCCC 3000

AGGCCAAGCC GGGAACCCCG GGTGGGACAG GAGGACCGGC CCCGCAGTAC 3050

TGACCTGCAG GAACTCCCCA CCCCAGGGAC ACCGCCTCCC CATTTTCCGG 3100

GGCAGAGTGG GGACTCACAG AGGCCCCCAG CCCTGTGCCC CGCTGGATTG 3150

CACTTTGAGC CCGTGGGGTG AGGAGTTGGC AATTTGGAGA GACAGGATTT 3200

GGGGGTTCTG CCATAATAGG AGGGGAAAAT CACCCCCCAG CCACCTCGGG 3250

GAACTCCAGA CCAAGGGTGA GGGCGCCTTT CCCTCAGGAC TGGGTGTGAC 3300

CAGAGGAAAA GGAAGTGCCC AACATCTCCC AGCCTCCCCA GGTGCCCCCC 3350

TCACCTTGAT GGGTGCGTTC CCGCAGACCA AAGAGAGTGT GACTCCCTTG 3400

CCAGCTCCAG AGTGGGGGGG CTGTCCCAGG GGGCAAGAAG GGGTGTCAGG 3450

GCCCAGTGAC AAAATCATTG GGGTTTGTAG TCCCAACTTG CTGCTGTCAC 3500

CACCAAACTC AATCATTTTT TTCCCTTGTA AATGCCCCTC CCCCAGCTGC 3550

TGCCTTCATA TTGAAGGTTT TTGAGTTTTG TTTTTGGTCT TAATTTTTCT 3600

CCCCGTTCCC TTTTTGTTTC TTCGTTTTGT TTTTCTACCG TCCTTGTCAT 3650

AACTTTGTGT TGGAGGGAAC CTGTTTCACT ATGGCCTCCT TTGCCCAAGT 3700

TGAAACAGGG GCCCATCATC ATGTCTGTTT CCAGAACAGT GCCTTGGTCA 3750

TCCCACATCC CCGGACCCCG CCTGGGACCC CCAAGCTGTG TCCTATGAAG 3800

GGGTGTGGGG TGAGGTAGTG AAAAGGGCGG TAGTTGGTGG TGGAACCCAG 3850

AAACGGACGC CGGTGCTTGG AGGGGTTCTT AAATTATATT TAAAAAAGTA 3900

ACTTTTTGTA TAAATAAAAG AAAATGGGAC GTGTCCCAGC TCCAGGGGTA 3950

AAAAAAAAAA AAAAAAAAA 3969

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1276 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala
1 5 10 15

Leu Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu
20 25 30

Lys Trp Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu
35 40 45

Ser Gly Leu Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val
50 55 60

Cys Asp Val Gln Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr
65 70 75

Gly Trp Val Pro Arg Arg Gly Ala Val His Val Tyr Ala Thr Leu
80 85 90

Arg Phe Thr Met Leu Glu Cys Leu Ser Leu Pro Arg Ala Gly Arg
95 100 105

Ser Cys Lys Glu Thr Phe Thr Val Phe Tyr Tyr Glu Ser Asp Ala
110 115 120

Asp Thr Ala Thr Ala Leu Thr Pro Ala Trp Met Glu Asn Pro Tyr
125 130 135

Ile Lys Val Asp Thr Val Ala Ala Glu His Leu Thr Arg Lys Arg
140 145 150

Pro Gly Ala Glu Ala Thr Gly Lys Val Asn Val Lys Thr Leu Arg
155 160 165

Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala Phe Gln Asp
170 175 180

Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu Phe Tyr Lys
185 190 195

Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro Glu Thr
200 205 210

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Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val Val
                215                 220                 225

Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
                230                 235                 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys
                245                 250                 255

Ala Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala
                260                 265                 270

Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys
                275                 280                 285

Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala
                290                 295                 300

Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro
                305                 310                 315

Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg Ser Val
                320                 325                 330

Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser Ala
                335                 340                 345

Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg
                350                 355                 360

Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly
                365                 370                 375

Asp Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp
                380                 385                 390

Val Val Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu
                395                 400                 405

Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val
                410                 415                 420

Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro
                425                 430                 435

Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser Ser Leu
                440                 445                 450

Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val Leu
                455                 460                 465

Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
                470                 475                 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg
                485                 490                 495
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Gly Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg
500 505 510

Ser Glu Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln
515 520 525

Thr Gln Leu Asp Glu Ser Glu Gly Trp Arg Glu Gln Leu Ala Leu
530 535 540

Ile Ala Gly Thr Ala Val Val Gly Val Val Leu Val Leu Val Val
545 550 555

Ile Val Val Ala Val Leu Cys Leu Arg Lys Gln Ser Asn Gly Arg
560 565 570

Glu Ala Glu Tyr Ser Asp Lys His Gly Gln Tyr Leu Ile Gly His
575 580 585

Gly Thr Lys Val Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn
590 595 600

Glu Ala Val Arg Glu Phe Ala Lys Glu Ile Asp Val Ser Tyr Val
605 610 615

Lys Ile Glu Glu Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys
620 625 630

Arg Gly Arg Leu Lys Ala Pro Gly Lys Lys Glu Ser Cys Val Ala
635 640 645

Ile Lys Thr Leu Lys Gly Gly Tyr Thr Glu Arg Gln Arg Arg Glu
650 655 660

Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Glu His Pro Asn
665 670 675

Ile Ile Arg Leu Glu Gly Val Val Thr Asn Ser Met Pro Val Met
680 685 690

Ile Leu Thr Glu Phe Met Glu Asn Gly Ala Leu Asp Ser Phe Leu
695 700 705

Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met
710 715 720

Leu Arg Gly Ile Ala Ser Gly Met Arg Tyr Leu Ala Glu Met Ser
725 730 735

Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
740 745 750

Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu
755 760 765

Glu Glu Asn Ser Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly
770 775 780

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Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg
                785                 790                 795

Lys Phe Thr Ser Ala Ser Asp Ala Trp Ser Tyr Gly Ile Val Met
                800                 805                 810

Trp Glu Val Met Ser Phe Gly Glu Arg Pro Tyr Trp Asp Met Ser
                815                 820                 825

Asn Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro
                830                 835                 840

Pro Pro Pro Asp Cys Pro Thr Ser Leu His Gln Leu Met Leu Asp
                845                 850                 855

Cys Trp Gln Lys Asp Arg Asn Ala Arg Pro Arg Phe Pro Gln Val
                860                 865                 870

Val Ser Ala Leu Asp Lys Met Ile Arg Asn Pro Ala Ser Leu Lys
                875                 880                 885

Ile Val Ala Arg Glu Asn Gly Gly Ala Ser His Pro Leu Leu Asp
                890                 895                 900

Gln Arg Gln Pro His Tyr Ser Ala Phe Gly Ser Val Gly Glu Trp
                905                 910                 915

Leu Arg Ala Ile Lys Met Gly Arg Tyr Glu Glu Ser Phe Ala Ala
                920                 925                 930

Ala Gly Phe Gly Ser Phe Glu Leu Val Ser Gln Ile Ser Ala Glu
                935                 940                 945

Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln Lys Lys
                950                 955                 960

Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly
                965                 970                 975

Thr Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr Pro Ala Gly
                980                 985                 990

Thr Pro His Pro Arg Asp Thr Ala Ser Pro Phe Ser Gly Ala Glu
                995                1000                1005

Trp Gly Leu Thr Glu Ala Pro Ser Pro Val Pro Arg Trp Ile Ala
               1010                1015                1020

Leu Ala Arg Gly Val Arg Ser Trp Gln Phe Gly Glu Thr Gly Phe
               1025                1030                1035

Gly Gly Ser Ala Ile Ile Gly Gly Glu Asn His Pro Pro Ala Thr
               1040                1045                1050

Ser Gly Asn Ser Arg Pro Arg Val Arg Ala Pro Phe Pro Gln Asp
               1055                1060                1065
```

```
Trp Val Pro Glu Glu Lys Glu Val Pro Asn Ile Ser Gln Pro Pro
                1070                1075                1080

Gln Val Pro Pro Ser Pro Trp Val Arg Ser Arg Arg Pro Lys Arg
                1085                1090                1095

Val Leu Pro Cys Gln Leu Gln Ser Gly Gly Ala Val Pro Gly Gly
                1100                1105                1110

Lys Lys Gly Cys Gln Gly Pro Val Thr Lys Ser Leu Gly Phe Val
                1115                1120                1125

Val Pro Thr Cys Cys Cys His His Gln Thr Gln Ser Phe Phe Ser
                1130                1135                1140

Leu Val Asn Ala Pro Pro Pro Ala Ala Ala Phe Ile Leu Lys Val
                1145                1150                1155

Phe Glu Phe Cys Phe Trp Ser Phe Phe Ser Pro Phe Pro Phe Cys
                1160                1165                1170

Phe Phe Val Leu Phe Phe Tyr Arg Pro Cys His Asn Phe Val Leu
                1175                1180                1185

Glu Gly Thr Cys Phe Thr Met Ala Ser Phe Ala Gln Val Glu Thr
                1190                1195                1200

Gly Ala His His His Val Cys Phe Gln Asn Ser Ala Leu Val Ile
                1205                1210                1215

Pro His Pro Arg Thr Pro Pro Gly Thr Pro Lys Leu Cys Pro Met
                1220                1225                1230

Lys Gly Cys Gly Val Arg Lys Gly Arg Leu Val Val Glu Pro Arg
                1235                1240                1245

Asn Gly Arg Arg Cys Leu Glu Gly Phe Leu Asn Tyr Ile Lys Ser
                1250                1255                1260

Asn Phe Leu Tyr Lys Lys Lys Met Gly Arg Val Pro Ala Pro Gly
                1265                1270                1275

Val
1276
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
 1               5                  10                  15
```

Asp Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro
20 25 30

Thr Tyr Thr Ser Ala Leu Gly Gly Lys Ile Pro Met Arg Trp Thr
35 40 45

Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Ala Ser Ala Ser
50 55 59

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
1 5 10 15

Gly Leu Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala
20 25 30

Asp Gly Gly Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile
35 40 45

His Tyr Arg Lys Phe Thr His Gln Ser
50 54

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Asn Cys Met Leu Ala Gly Asp Met Thr Val Cys Val Ala Asp Phe
1 5 10 15

Gly Leu Ser Trp Lys Ile Tyr Ser Gly Ala Thr Ile Val Arg Gly
20 25 30

Cys Ala Ser Lys Leu Pro Val Lys Trp Leu Ala Leu Gly Ser Leu
35 40 45

Ala Asp Asn Leu Tyr Thr Val His Ser
50 54

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Asn Cys Leu Val Gly Lys Asn Tyr Thr Ile Lys Ile Ala Asp Phe
1 5 10 15

Gly Met Ser Arg Asn Leu Tyr Ser Gly Asp Tyr Tyr
20 25 27

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile Gly
1 5 10 15

Asp Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr
20 25 30

Lys Val Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro
35 40 45

Glu Ser Leu Thr Glu Ser Leu Phe Ser Val Ala Ser Asp
50 55 58

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser
1 5 10 15

Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala
20 25 30

Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro
35 40 45

Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp
50 55 58

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4425 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TCGGGTCGGA CCCACGCGCA GCGGCCGGAG ATGCAGCGGG GCGCCGCGCT 50

GTGCCTGCGA CTGTGGCTCT GCCTGGGACT CCTGGACGGC CTGGTGAGTG 100

GCTACTCCAT GACCCCCCCG ACCTTGAACA TCACGGAGGA GTCACACGTC 150

ATCGACACCG GTGACAGCCT GTCCATCTCC TGCAGGGGAC AGCACCCCCT 200

CGAGTGGGCT TGGCCAGGAG CTCAGGAGGC GCCAGCCACC GGAGACAAGG 250

ACAGCGAGGA CACGGGGGTG GTGCGAGACT GCGAGGGCAC AGACGCCAGG 300

CCCTACTGCA AGGTGTTGCT GCTGCACGAG GTACATGCCA ACGACACAGG 350

CAGCTACGTC TGCTACTACA AGTACATCAA GGCACGCATC GAGGGCACCA 400

CGGCCGCCAG CTCCTACGTG TTCGTGAGAG ACTTTGAGCA GCCATTCATC 450

AACAAGCCTG ACACGCTCTT GGTCAACAGG AAGGACGCCA TGTGGGTGCC 500

CTGTCTGGTG TCCATCCCCG GCCTCAATGT CACGCTGCGC TCGCAAAGCT 550

CGGTGCTGTG GCCAGACGGG CAGGAGGTGG TGTGGGATGA CCGGCGGGGC 600

ATGCTCGTGT CCACGCCACT GCTGCACGAT GCCCTGTACC TGCAGTGCGA 650

GACCACCTGG GGAGACCAGG ACTTCCTTTC CAACCCCTTC CTGGTGCACA 700

TCACAGGCAA CGAGCTCTAT GACATCCAGC TGTTGCCCAG GAAGTCGCTG 750

GAGCTGCTGG TAGGGGAGAA GCTGGTCCTG AACTGCACCG TGTGGGCTGA 800

GTTTAACTCA GGTGTCACCT TTGACTGGGA CTACCCAGGG AAGCAGGCAG 850

AGCGGGGTAA GTGGGTGCCC GAGCGACGCT CCCAGCAGAC CCACACAGAA 900

CTCTCCAGCA TCCTGACCAT CCACAACGTC AGCCAGCACG ACCTGGGCTC 950

GTATGTGTGC AAGGCCAACA ACGGCATCCA GCGATTTCGG GAGAGCACCG 1000

AGGTCATTGT GCATGAAAAT CCCTTCATCA GCGTCGAGTG GCTCAAAGGA 1050

CCCATCCTGG AGGCCACGGC AGGAGACGAG CTGGTGAAGC TGCCCGTGAA 1100

GCTGGCAGCG TACCCCCCGC CCGAGTTCCA GTGGTACAAG GATGGAAAGG 1150

CACTGTCCGG GCGCCACAGT CCACATGCCC TGGTGCTCAA GGAGGTGACA 1200

GAGGCCAGCA CAGGCACCTA CACCCTCGCC CTGTGGAACT CCGCTGCTGG 1250

CCTGAGGCGC AACATCAGCC TGGAGCTGGT GGTGAATGTG CCCCCCCAGA 1300

TACATGAGAA GGAGGCCTCC TCCCCCAGCA TCTACTCGCG TCACAGCCGC 1350

CAGGCCCTCA CCTGCACGGC CTACGGGGTG CCCCTGCCTC TCAGCATCCA 1400

GTGGCACTGG CGGCCCTGGA CACCCTGCAA GATGTTTGCC CAGCGTAGTC 1450

TCCGGCGGCG GCAGCAGCAA GACCTCATGC CACAGTGCCG TGACTGGAGG 1500

GCGGTGACCA CGCAGGATGC CGTGAACCCC ATCGAGAGCC TGGACACCTG 1550

GACCGAGTTT GTGGAGGGAA AGAATAAGAC TGTGAGCAAG CTGGTGATCC 1600

AGAATGCCAA CGTGTCTGCC ATGTACAAGT GTGTGGTCTC CAACAAGGTG 1650

GGCCAGGATG AGCGGCTCAT CTACTTCTAT GTGACCACCA TCCCCGACGG 1700

CTTCACCATC GAATCCAAGC CATCCGAGGA GCTACTAGAG GGCCAGCCGG 1750

TGCTCCTGAG CTGCCAAGCC GACAGCTACA AGTACGAGCA TCTGCGCTGG 1800

TACCGCCTCA ACCTGTCCAC GCTGCACGAT GCGCACGGGA ACCCGCTTCT 1850

GCTCGACTGC AAGAACGTGC ATCTGTTCGC CACCCCTCTG GCCGCCAGCC 1900

TGGAGGAGGT GGCACCTGGG GCGCGCCACG CCACGCTCAG CCTGAGTATC 1950

CCCCGCGTCG CGCCCGAGCA CGAGGGCCAC TATGTGTGCG AAGTGCAAGA 2000

CCGGCGCAGC CATGACAAGC ACTGCCACAA GAAGTACCTG TCGGTGCAGG 2050

CCCTGGAAGC CCCTCGGCTC ACGCAGAACT TGACCGACCT CCTGGTGAAC 2100

GTGAGCGACT CGCTGGAGAT GCAGTGCTTG GTGGCCGGAG CGCACGCGCC 2150

CAGCATCGTG TGGTACAAAG ACGAGAGGCT GCTGGAGGAA AAGTCTGGAG 2200

TCGACTTGGC GGACTCCAAC CAGAAGCTGA GCATCCAGCG CGTGCGCGAG 2250

GAGGATGCGG GACGCTATCT GTGCAGCGTG TGCAACGCCA AGGGCTGCGT 2300

CAACTCCTCC GCCAGCGTGG CCGTGGAAGG CTCCGAGGAT AAGGGCAGCA 2350

TGGAGATCGT GATCCTTGTC GGTACCGGCG TCATCGCTGT CTTCTTCTGG 2400

GTCCTCCTCC TCCTCATCTT CTGTAACATG AGGAGGCCGG CCCACGCAGA 2450

CATCAAGACG GGCTACCTGT CCATCATCAT GGACCCCGGG GAGGTGCCTC 2500

TGGAGGAGCA ATGCGAATAC CTGTCCTACG ATGCCAGCCA GTGGGAATTC 2550

CCCCGAGAGC GGCTGCACCT GGGGAGAGTG CTCGGCTACG GCGCCTTCGG 2600

GAAGGTGGTG GAAGCCTCCG CTTTCGGCAT CCACAAGGGC AGCAGCTGTG 2650

ACACCGTGGC CGTGAAAATG CTGAAAGAGG GCGCCACGGC CAGCGAGCAC 2700

CGCGCGCTGA TGTCGGAGCT CAAGATCCTC ATTCACATCG GCAACCACCT 2750

CAACGTGGTC AACCTCCTCG GGGCGTGCAC CAAGCCGCAG GGCCCCCTCA 2800

TGGTGATCGT GGAGTTCTGC AAGTACGGCA ACCTCTCCAA CTTCCTGCGC 2850

GCCAAGCGGG ACGCCTTCAG CCCCTGCGCG GAGAAGTCTC CCGAGCAGCG 2900

CGGACGCTTC CGCGCCATGG TGGAGCTCGC CAGGCTGGAT CGGAGGCGGC 2950

CGGGGAGCAG CGACAGGGTC CTCTTCGCGC GGTTCTCGAA GACCGAGGGC 3000

GGAGCGAGGC GGGCTTCTCC AGACCAAGAA GCTGAGGACC TGTGGCTGAG 3050

CCCGCTGACC ATGGAAGATC TTGTCTGCTA CAGCTTCCAG GTGGCCAGAG 3100

GGATGGAGTT CCTGGCTTCC CGAAAGTGCA TCCACAGAGA CCTGGCTGCT 3150

CGGAACATTC TGCTGTCGGA AAGCGACGTG GTGAAGATCT GTGACTTTGG 3200

CCTTGCCCGG GACATCTACA AAGACCCTGA CTACGTCCGC AAGGGCAGTG 3250

CCCGGCTGCC CCTGAAGTGG ATGGCCCCTG AAAGCATCTT CGACAAGGTG 3300

TACACCACGC AGAGTGACGT GTGGTCCTTT GGGGTGCTTC TCTGGGAGAT 3350

CTTCTCTCTG GGGGCCTCCC CGTACCCTGG GGTGCAGATC AATGAGGAGT 3400

TCTGCCAGCG GCTGAGAGAC GGCACAAGGA TGAGGGCCCC GGAGCTGGCC 3450

ACTCCCGCCA TACGCCGCAT CATGCTGAAC TGCTGGTCCG GAGACCCCAA 3500

GGCGAGACCT GCATTCTCGG AGCTGGTGGA GATCCTGGGG GACCTGCTCC 3550

AGGGCAGGGG CCTGCAAGAG GAAGAGGAGG TCTGCATGGC CCCGCGCAGC 3600

TCTCAGAGCT CAGAAGAGGG CAGCTTCTCG CAGGTGTCCA CCATGGCCCT 3650

ACACATCGCC CAGGCTGACG CTGAGGACAG CCCGCCAAGC CTGCAGCGCC 3700

ACAGCCTGGC CGCCAGGTAT TACAACTGGG TGTCCTTTCC CGGGTGCCTG 3750

GCCAGAGGGG CTGAGACCCG TGGTTCCTCC AGGATGAAGA CATTTGAGGA 3800

ATTCCCCATG ACCCCAACGA CCTACAAAGG CTCTGTGGAC AACCAGACAG 3850

ACAGTGGGAT GGTGCTGGCC TCGGAGGAGT TTGAGCAGAT AGAGAGCAGG 3900

CATAGACAAG AAAGCGGCTT CAGGTAGCTG AAGCAGAGAG AGAGAAGGCA 3950

GCATACGTCA GCATTTTCTT CTCTGCACTT ATAAGAAAGA TCAAAGACTT 4000

TAAGACTTTC GCTATTTCTT CTGCTATCTA CTACAAACTT CAAAGAGGAA 4050

CCAGGAGGCC AAGAGGAGCA TGAAAGTGGA CAAGGAGTGT GACCACTGAA 4100

GCACCACAGG GAGGGGTTAG GCCTCCGGAT GACTGCGGGC AGGCCTGGAT 4150

AATATCCAGC CTCCCACAAG AAGCTGGTGG AGCAGAGTGT TCCCTGACTC 4200

CTCCAAGGAA AGGGAGACGC CCTTTCATGG TCTGCTGAGT AACAGGTGCC 4250

TTCCCAGACA CTGGCGTTAC TGCTTGACCA AAGAGCCCTC AAGCGGCCCT 4300

TATGCCAGCG TGACAGAGGG CTCACCTCTT GCCTTCTAGG TCACTTCTCA 4350

CAATGTCCCT TCAGCACCTG ACCCTGTGCC CGCCAGTTAT TCCTTGGTAA 4400

TATGAGTAAT ACATCAAAGA GTAGT 4425

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4425 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

AGCCCAGCCT GGGTGCGCGT CGCCGGCCTC TACGTCGCCC CGCGGCGCGA 50

CACGGACGCT GACACCGAGA CGGACCCTGA GGACCTGCCG GACCACTCAC 100

CGATGAGGTA CTGGGGGGGC TGGAACTTGT AGTGCCTCCT CAGTGTGCAG 150

TAGCTGTGGC CACTGTCGGA CAGGTAGAGG ACGTCCCCTG TCGTGGGGGA 200

GCTCACCCGA ACCGGTCCTC GAGTCCTCCG CGGTCGGTGG CCTCTGTTCC 250

TGTCGCTCCT GTGCCCCCAC CACGCTCTGA CGCTCCCGTG TCTGCGGTCC 300

GGGATGACGT TCCACAACGA CGACGTGCTC CATGTACGGT TGCTGTGTCC 350

GTCGATGCAG ACGATGATGT TCATGTAGTT CCGTGCGTAG CTCCCGTGGT 400

GCCGGCGGTC GAGGATGCAC AAGCACTCTC TGAAACTCGT CGGTAAGTAG 450

TTGTTCGGAC TGTGCGAGAA CCAGTTGTCC TTCCTGCGGT ACACCCACGG 500

GACAGACCAC AGGTAGGGGC CGGAGTTACA GTGCGACGCG AGCGTTTCGA 550

GCCACGACAC CGGTCTGCCC GTCCTCCACC ACACCCTACT GGCCGCCCCG 600

TACGAGCACA GGTGCGGTGA CGACGTGCTA CGGGACATGG ACGTCACGCT 650

CTGGTGGACC CCTCTGGTCC TGAAGGAAAG GTTGGGGAAG GACCACGTGT 700

AGTGTCCGTT GCTCGAGATA CTGTAGGTCG ACAACGGGTC CTTCAGCGAC 750

CTCGACGACC ATCCCCTCTT CGACCAGGAC TTGACGTGGC ACACCCGACT 800

CAAATTGAGT CCACAGTGGA AACTGACCCT GATGGGTCCC TTCGTCCGTC 850

TCGCCCCATT CACCCACGGG CTCGCTGCGA GGGTCGTCTG GGTGTGTCTT 900

GAGAGGTCGT AGGACTGGTA GGTGTTGCAG TCGGTCGTGC TGGACCCGAG 950

CATACACACG TTCCGGTTGT TGCCGTAGGT CGCTAAAGCC CTCTCGTGGC 1000

TCCAGTAACA CGTACTTTTA GGGAAGTAGT CGCAGCTCAC CGAGTTTCCT 1050

GGGTAGGACC TCCGGTGCCG TCCTCTGCTC GACCACTTCG ACGGGCACTT 1100

CGACCGTCGC ATGGGGGGCG GGCTCAAGGT CACCATGTTC CTACCTTTCC 1150

GTGACAGGCC CGCGGTGTCA GGTGTACGGG ACCACGAGTT CCTCCACTGT 1200

CTCCGGTCGT GTCCGTGGAT GTGGGAGCGG GACACCTTGA GGCGACGACC 1250

GGACTCCGCG TTGTAGTCGG ACCTCGACCA CCACTTACAC GGGGGGGTCT 1300

ATGTACTCTT CCTCCGGAGG AGGGGGTCGT AGATGAGCGC AGTGTCGGCG 1350

GTCCGGGAGT GGACGTGCCG GATGCCCCAC GGGGACGGAG AGTCGTAGGT 1400

CACCGTGACC GCCGGGACCT GTGGGACGTT CTACAAACGG GTCGCATCAG 1450

AGGCCGCCGC CGTCGTCGTT CTGGAGTACG GTGTCACGGC ACTGACCTCC 1500

CGCCACTGGT GCGTCCTACG GCACTTGGGG TAGCTCTCGG ACCTGTGGAC 1550

CTGGCTCAAA CACCTCCCTT TCTTATTCTG ACACTCGTTC GACCACTAGG 1600

TCTTACGGTT GCACAGACGG TACATGTTCA CACACCAGAG GTTGTTCCAC 1650

CCGGTCCTAC TCGCCGAGTA GATGAAGATA CACTGGTGGT AGGGGCTGCC 1700

GAAGTGGTAG CTTAGGTTCG GTAGGCTCCT CGATGATCTC CCGGTCGGCC 1750

ACGAGGACTC GACGGTTCGG CTGTCGATGT TCATGCTCGT AGACGCGACC 1800

ATGGCGGAGT TGGACAGGTG CGACGTGCTA CGCGTGCCCT TGGGCGAAGA 1850

CGAGCTGACG TTCTTGCACG TAGACAAGCG GTGGGGAGAC CGGCGGTCGG 1900

ACCTCCTCCA CCGTGGACCC CGCGCGGTGC GGTGCGAGTC GGACTCATAG 1950

GGGGCGCAGC GCGGGCTCGT GCTCCCGGTG ATACACACGC TTCACGTTCT 2000

GGCCGCGTCG GTACTGTTCG TGACGGTGTT CTTCATGGAC AGCCACGTCC 2050

GGGACCTTCG GGGAGCCGAG TGCGTCTTGA ACTGGCTGGA GGACCACTTG 2100

CACTCGCTGA GCGACCTCTA CGTCACGAAC CACCGGCCTC GCGTGCGCGG 2150

GTCGTAGCAC ACCATGTTTC TGCTCTCCGA CGACCTCCTT TTCAGACCTC 2200

AGCTGAACCG CCTGAGGTTG GTCTTCGACT CGTAGGTCGC GCACGCGCTC 2250

CTCCTACGCC CTGCGATAGA CACGTCGCAC ACGTTGCGGT TCCCGACGCA 2300

GTTGAGGAGG CGGTCGCACC GGCACCTTCC GAGGCTCCTA TTCCCGTCGT 2350

ACCTCTAGCA CTAGGAACAG CCATGGCCGC AGTAGCGACA GAAGAAGACC 2400

CAGGAGGAGG AGGAGTAGAA GACATTGTAC TCCTCCGGCC GGGTGCGTCT 2450

GTAGTTCTGC CCGATGGACA GGTAGTAGTA CCTGGGGCCC CTCCACGGAG 2500

ACCTCCTCGT TACGCTTATG GACAGGATGC TACGGTCGGT CACCCTTAAG 2550

GGGGCTCTCG CCGACGTGGA CCCCTCTCAC GAGCCGATGC CGCGGAAGCC 2600

CTTCCACCAC CTTCGGAGGC GAAAGCCGTA GGTGTTCCCG TCGTCGACAC 2650

TGTGGCACCG GCACTTTTAC GACTTTCTCC CGCGGTGCCG GTCGCTCGTG 2700

GCGCGCGACT ACAGCCTCGA GTTCTAGGAG TAAGTGTAGC CGTTGGTGGA 2750

GTTGCACCAG TTGGAGGAGC CCCGCACGTG GTTCGGCGTC CCGGGGGAGT 2800

ACCACTAGCA CCTCAAGACG TTCATGCCGT TGGAGAGGTT GAAGGACGCG 2850

CGGTTCGCCC TGCGGAAGTC GGGGACGCGC CTCTTCAGAG GGCTCGTCGC 2900

GCCTGCGAAG GCGCGGTACC ACCTCGAGCG GTCCGACCTA GCCTCCGCCG 2950

GCCCCTCGTC GCTGTCCCAG GAGAAGCGCG CCAAGAGCTT CTGGCTCCCG 3000

CCTCGCTCCG CCCGAAGAGG TCTGGTTCTT CGACTCCTGG ACACCGACTC 3050

GGGCGACTGG TACCTTCTAG AACAGACGAT GTCGAAGGTC CACCGGTCTC 3100

CCTACCTCAA GGACCGAAGG GCTTTCACGT AGGTGTCTCT GGACCGACGA 3150

GCCTTGTAAG ACGACAGCCT TTCGCTGCAC CACTTCTAGA CACTGAAACC 3200

GGAACGGGCC CTGTAGATGT TTCTGGGACT GATGCAGGCG TTCCCGTCAC 3250

GGGCCGACGG GGACTTCACC TACCGGGGAC TTTCGTAGAA GCTGTTCCAC 3300

ATGTGGTGCG TCTCACTGCA CACCAGGAAA CCCCACGAAG AGACCCTCTA 3350

GAAGAGAGAC CCCCGGAGGG GCATGGGACC CCACGTCTAG TTACTCCTCA 3400

AGACGGTCGC CGACTCTCTG CCGTGTTCCT ACTCCCGGGG CCTCGACCGG 3450

TGAGGGCGGT ATGCGGCGTA GTACGACTTG ACGACCAGGC CTCTGGGGTT 3500

CCGCTCTGGA CGTAAGAGCC TCGACCACCT CTAGGACCCC CTGGACGAGG 3550

TCCCGTCCCC GGACGTTCTC CTTCTCCTCC AGACGTACCG GGGCGCGTCG 3600

AGAGTCTCGA GTCTTCTCCC GTCGAAGAGC GTCCACAGGT GGTACCGGGA 3650

TGTGTAGCGG GTCCGACTGC GACTCCTGTC GGGCGGTTCG GACGTCGCGG 3700

TGTCGGACCG GCGGTCCATA ATGTTGACCC ACAGGAAAGG GCCCACGGAC 3750

CGGTCTCCCC GACTCTGGGC ACCAAGGAGG TCCTACTTCT GTAAACTCCT 3800

TAAGGGGTAC TGGGGTTGCT GGATGTTTCC GAGACACCTG TTGGTCTGTC 3850

TGTCACCCTA CCACGACCGG AGCCTCCTCA AACTCGTCTA TCTCTCGTCC 3900

GTATCTGTTC TTTCGCCGAA GTCCATCGAC TTCGTCTCTC TCTCTTCCGT 3950

CGTATGCAGT CGTAAAAGAA GAGACGTGAA TATTCTTTCT AGTTTCTGAA 4000

ATTCTGAAAG CGATAAAGAA GACGATAGAT GATGTTTGAA GTTTCTCCTT 4050

GGTCCTCCGG TTCTCCTCGT ACTTTCACCT GTTCCTCACA CTGGTGACTT 4100

CGTGGTGTCC CTCCCCAATC CGGAGGCCTA CTGACGCCCG TCCGGACCTA 4150

TTATAGGTCG GAGGGTGTTC TTCGACCACC TCGTCTCACA AGGGACTGAG 4200

GAGGTTCCTT TCCCTCTGCG GGAAAGTACC AGACGACTCA TTGTCCACGG 4250

AAGGGTCTGT GACCGCAATG ACGAACTGGT TTCTCGGGAG TTCGCCGGGA 4300

ATACGGTCGC ACTGTCTCCC GAGTGGAGAA CGGAAGATCC AGTGAAGAGT 4350

GTTACAGGGA AGTCGTGGAC TGGGACACGG GCGGTCAATA AGGAACCATT 4400

ATACTCATTA TGTAGTTTCT CATCA 4425

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1298 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu
1 5 10 15

Gly Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr Pro Pro
20 25 30

Thr Leu Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp
35 40 45

Ser Leu Ser Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala
50 55 60

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Trp Pro Gly Ala Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser
                65                  70                  75

Glu Asp Thr Gly Val Val Arg Asp Cys Glu Gly Thr Asp Ala Arg
                80                  85                  90

Pro Tyr Cys Lys Val Leu Leu Leu His Glu Val His Ala Asn Asp
                95                 100                 105

Thr Gly Ser Tyr Val Cys Tyr Tyr Lys Tyr Ile Lys Ala Arg Ile
               110                 115                 120

Glu Gly Thr Thr Ala Ala Ser Ser Tyr Val Phe Val Arg Asp Phe
               125                 130                 135

Glu Gln Pro Phe Ile Asn Lys Pro Asp Thr Leu Leu Val Asn Arg
               140                 145                 150

Lys Asp Ala Met Trp Val Pro Cys Leu Val Ser Ile Pro Gly Leu
               155                 160                 165

Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu Trp Pro Asp Gly
               170                 175                 180

Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu Val Ser Thr
               185                 190                 195

Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr Thr Trp
               200                 205                 210

Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile Thr
               215                 220                 225

Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu Pro Arg Lys Ser Leu
               230                 235                 240

Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp
               245                 250                 255

Ala Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr Pro Gly
               260                 265                 270

Lys Gln Ala Glu Arg Gly Lys Trp Val Pro Glu Arg Arg Ser Gln
               275                 280                 285

Gln Thr His Thr Glu Leu Ser Ser Ile Leu Thr Ile His Asn Val
               290                 295                 300

Ser Gln His Asp Leu Gly Ser Tyr Val Cys Lys Ala Asn Asn Gly
               305                 310                 315

Ile Gln Arg Phe Arg Glu Ser Thr Glu Val Ile Val His Glu Asn
               320                 325                 330

Pro Phe Ile Ser Val Glu Trp Leu Lys Gly Pro Ile Leu Glu Ala
               335                 340                 345
```

Thr Ala Gly Asp Glu Leu Val Lys Leu Pro Val Lys Leu Ala Ala
350 355 360

Tyr Pro Pro Pro Glu Phe Gln Trp Tyr Lys Asp Gly Lys Ala Leu
365 370 375

Ser Gly Arg His Ser Pro His Ala Leu Val Leu Lys Glu Val Thr
380 385 390

Glu Ala Ser Thr Gly Thr Tyr Thr Leu Ala Leu Trp Asn Ser Ala
395 400 405

Ala Gly Leu Arg Arg Asn Ile Ser Leu Glu Leu Val Val Asn Val
410 415 420

Pro Pro Gln Ile His Glu Lys Glu Ala Ser Ser Pro Ser Ile Tyr
425 430 435

Ser Arg His Ser Arg Gln Ala Leu Thr Cys Thr Ala Tyr Gly Val
440 445 450

Pro Leu Pro Leu Ser Ile Gln Trp His Trp Arg Pro Trp Thr Pro
455 460 465

Cys Lys Met Phe Ala Gln Arg Ser Leu Arg Arg Arg Gln Gln Gln
470 475 480

Asp Leu Met Pro Gln Cys Arg Asp Trp Arg Ala Val Thr Thr Gln
485 490 495

Asp Ala Val Asn Pro Ile Glu Ser Leu Asp Thr Trp Thr Glu Phe
500 505 510

Val Glu Gly Lys Asn Lys Thr Val Ser Lys Leu Val Ile Gln Asn
515 520 525

Ala Asn Val Ser Ala Met Tyr Lys Cys Val Val Ser Asn Lys Val
530 535 540

Gly Gln Asp Glu Arg Leu Ile Tyr Phe Tyr Val Thr Thr Ile Pro
545 550 555

Asp Gly Phe Thr Ile Glu Ser Lys Pro Ser Glu Glu Leu Leu Glu
560 565 570

Gly Gln Pro Val Leu Leu Ser Cys Gln Ala Asp Ser Tyr Lys Tyr
575 580 585

Glu His Leu Arg Trp Tyr Arg Leu Asn Leu Ser Thr Leu His Asp
590 595 600

Ala His Gly Asn Pro Leu Leu Leu Asp Cys Lys Asn Val His Leu
605 610 615

Phe Ala Thr Pro Leu Ala Ala Ser Leu Glu Glu Val Ala Pro Gly
620 625 630

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Ala Arg His Ala Thr Leu Ser Leu Ser Ile Pro Arg Val Ala Pro
635                 640                 645

Glu His Glu Gly His Tyr Val Cys Glu Val Gln Asp Arg Arg Ser
650                 655                 660

His Asp Lys His Cys His Lys Lys Tyr Leu Ser Val Gln Ala Leu
665                 670                 675

Glu Ala Pro Arg Leu Thr Gln Asn Leu Thr Asp Leu Leu Val Asn
680                 685                 690

Val Ser Asp Ser Leu Glu Met Gln Cys Leu Val Ala Gly Ala His
695                 700                 705

Ala Pro Ser Ile Val Trp Tyr Lys Asp Glu Arg Leu Leu Glu Glu
710                 715                 720

Lys Ser Gly Val Asp Leu Ala Asp Ser Asn Gln Lys Leu Ser Ile
725                 730                 735

Gln Arg Val Arg Glu Glu Asp Ala Gly Arg Tyr Leu Cys Ser Val
740                 745                 750

Cys Asn Ala Lys Gly Cys Val Asn Ser Ser Ala Ser Val Ala Val
755                 760                 765

Glu Gly Ser Glu Asp Lys Gly Ser Met Glu Ile Val Ile Leu Val
770                 775                 780

Gly Thr Gly Val Ile Ala Val Phe Phe Trp Val Leu Leu Leu Leu
785                 790                 795

Ile Phe Cys Asn Met Arg Arg Pro Ala His Ala Asp Ile Lys Thr
800                 805                 810

Gly Tyr Leu Ser Ile Ile Met Asp Pro Gly Glu Val Pro Leu Glu
815                 820                 825

Glu Gln Cys Glu Tyr Leu Ser Tyr Asp Ala Ser Gln Trp Glu Phe
830                 835                 840

Pro Arg Glu Arg Leu His Leu Gly Arg Val Leu Gly Tyr Gly Ala
845                 850                 855

Phe Gly Lys Val Val Glu Ala Ser Ala Phe Gly Ile His Lys Gly
860                 865                 870

Ser Ser Cys Asp Thr Val Ala Val Lys Met Leu Lys Glu Gly Ala
875                 880                 885

Thr Ala Ser Glu His Arg Ala Leu Met Ser Glu Leu Lys Ile Leu
890                 895                 900

Ile His Ile Gly Asn His Leu Asn Val Val Asn Leu Leu Gly Ala
905                 910                 915
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Cys Thr Lys Pro Gln Gly Pro Leu Met Val Ile Val Glu Phe Cys
                920                 925                 930

Lys Tyr Gly Asn Leu Ser Asn Phe Leu Arg Ala Lys Arg Asp Ala
                935                 940                 945

Phe Ser Pro Cys Ala Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe
                950                 955                 960

Arg Ala Met Val Glu Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly
                965                 970                 975

Ser Ser Asp Arg Val Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly
                980                 985                 990

Gly Ala Arg Arg Ala Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp
                995                1000                1005

Leu Ser Pro Leu Thr Met Glu Asp Leu Val Cys Tyr Ser Phe Gln
               1010                1015                1020

Val Ala Arg Gly Met Glu Phe Leu Ala Ser Arg Lys Cys Ile His
               1025                1030                1035

Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Ser Asp Val
               1040                1045                1050

Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp
               1055                1060                1065

Pro Asp Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp
               1070                1075                1080

Met Ala Pro Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser
               1085                1090                1095

Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu
               1100                1105                1110

Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile Asn Glu Glu Phe Cys
               1115                1120                1125

Gln Arg Leu Arg Asp Gly Thr Arg Met Arg Ala Pro Glu Leu Ala
               1130                1135                1140

Thr Pro Ala Ile Arg Arg Ile Met Leu Asn Cys Trp Ser Gly Asp
               1145                1150                1155

Pro Lys Ala Arg Pro Ala Phe Ser Glu Leu Val Glu Ile Leu Gly
               1160                1165                1170

Asp Leu Leu Gln Gly Arg Gly Leu Gln Glu Glu Glu Glu Val Cys
               1175                1180                1185

Met Ala Pro Arg Ser Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser
               1190                1195                1200
```

Gln Val Ser Thr Met Ala Leu His Ile Ala Gln Ala Asp Ala Glu
1205 1210 1215

Asp Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala Ala Arg Tyr
1220 1225 1230

Tyr Asn Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu
1235 1240 1245

Thr Arg Gly Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro Met
1250 1255 1260

Thr Pro Thr Thr Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser
1265 1270 1275

Gly Met Val Leu Ala Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg
1280 1285 1290

His Arg Gln Glu Ser Gly Phe Arg
1295 1298

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3348 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATGGCTGGGA TTTTCTATTT CGCCCTATTT TCGTGTCTCT TCGGGATTTG 50

CGACGCTGTC ACAGGTTCCA GGGTATACCC CGCGAATGAA GTTACCTTAT 100

TGGATTCCAG ATCTGTTCAG GGAGAACTTG GGTGGATAGC AAGCCCTCTG 150

GAAGGAGGGT GGGAGGAAGT GAGTATCATG GATGAAAAAA ATACACCAAT 200

CCGAACCTAC CAAGTGTGCA ATGTGATGGA ACCCAGCCAG AATAACTGGC 250

TACGAACTGA TTGGATCACC CGAGAAGGGG CTCAGAGGGT GTATATTGAG 300

ATTAAATTCA CCTTGAGGGA CTGCAATAGT CTTCCGGGCG TCATGGGGAC 350

TTGCAAGGAG ACGTTTAACC TGTACTACTA TGAATCAGAC AACGACAAAG 400

AGCGTTTCAT CAGAGAGAAC CAGTTTGTCA AAATTGACAC CATTGCTGCT 450

GATGAGAGCT TCACCCAAGT GGACATTGGT GACAGAATCA TGAAGCTGAA 500

CACCGAGATC CGGGATGTAG GGCCATTAAG CAAAAAGGGG TTTTACCTGG 550

CTTTTCAGGA TGTGGGGGCC TGCATCGCCC TGGTATCAGT CCGTGTGTTC 600

TATAAAAAGT GTCCACTCAC AGTCCGCAAT CTGGCCCAGT TTCCTGACAC 650

CATCACAGGG GCTGATACGT CTTCCCTGGT GGAAGTTCGA GGCTCCTGTG 700

TCAACAACTC AGAAGAGAAA GATGTGCCAA AAATGTACTG TGGGGCAGAT 750

GGTGAATGGC TGGTACCCAT TGGCAACTGC CTATGCAACG CTGGGCATGA 800

GGAGCGGAGC GGAGAATGCC AAGCTTGCAA AATTGGATAT TACAAGGCTC 850

TCTCCACGGA TGCCACCTGT GCCAAGTGCC CACCCCACAG CTACTCTGTC 900

TGGGAAGGAG CCACCTCGTG CACCTGTGAC CGAGGCTTTT TCAGAGCTGA 950

CAACGATGCT GCCTCTATGC CCTGCACCCG TCCACCATCT GCTCCCCTGA 1000

ACTTGATTTC AAATGTCAAC GAGACATCTG TGAACTTGGA ATGGAGTAGC 1050

CCTCAGAATA CAGGTGGCCG CCAGGACATT TCCTATAATG TGGTATGCAA 1100

GAAATGTGGA GCTGGTGACC CCAGCAAGTG CCGACCCTGT GGAAGTGGGG 1150

TCCACTACAC CCCACAGCAG AATGGCTTGA AGACCACCAA AGGCTCCATC 1200

ACTGACCTCC TAGCTCATAC CAATTACACC TTTGAAATCT GGGCTGTGAA 1250

TGGAGTGTCC AAATATAACC CTAACCCAGA CCAATCAGTT TCTGTCACTG 1300

TGACCACCAA CCAAGCAGCA CCATCATCCA TTGCTTTGGT CCAGGCTAAA 1350

GAAGTCACAA GATACAGTGT GGCACTGGCT TGGCTGGAAC CAGATCGGCC 1400

CAATGGGGTA ATCCTGGAAT ATGAAGTCAA GTATTATGAG AAGGATCAGA 1450

ATGAGCGAAG CTATCGTATA GTTCGGACAG CTGCCAGGAA CACAGATATC 1500

AAAGGCCTGA ACCCTCTCAC TTCCTATGTT TTCCACGTGC GAGCCAGGAC 1550

AGCAGCTGGC TATGGAGACT TCAGTGAGCC CTTGGAGGTT ACAACCAACA 1600

CAGTGCCTTC CCGGATCATT GGAGATGGGG CTAACTCCAC AGTCCTTCTG 1650

GTCTCTGTCT CGGGCAGTGT GGTGCTGGTG GTAATTCTCA TTGCAGCTTT 1700

TGTCATCAGC CGGAGACGGA GTAAATACAG TAAAGCCAAA CAAGAAGCGG 1750

ATGAAGAGAA ACATTTGAAT CAAGGTGTAA GAACATATGT GGACCCCTTT 1800

ACGTACGAAG ATCCCAACCA AGCAGTGCGA GAGTTTGCCA AAGAAATTGA 1850

CGCATCCTGC ATTAAGATTG AAAAAGTTAT AGGAGTTGGT GAATTTGGTG 1900

AGGTATGCAG TGGGCGTCTC AAAGTGCCTG GCAAGAGAGA GATCTGTGTG 1950

GCTATCAAGA CTCTGAAAGC TGGTTATACA GACAAACAGA GGAGAGACTT 2000

CCTGAGTGAG GCCAGCATCA TGGGACAGTT TGACCATCCG AACATCATTC 2050

ACTTGGAAGG CGTGGTCACT AAATGTAAAC CAGTAATGAT CATAACAGAG 2100

TACATGGAGA ATGGCTCCTT GGATGCATTC CTCAGGAAAA ATGATGGCAG 2150

ATTTACAGTC ATTCAGCTGG TGGGCATGCT TCGTGGCATT GGGTCTGGGA 2200

TGAAGTATTT ATCTGATATG AGCTATGTGC ATCGTGATCT GGCCGCACGG 2250

AACATCCTGG TGAACAGCAA CTTGGTCTGC AAAGTGTCTG ATTTTGGCAT 2300

GTCCCGAGTG CTTGAGGATG ATCCGGAAGC AGCTTACACC ACCAGGGGTG 2350

GCAAGATTCC TATCCGGTGG ACTGCGCCAG AAGCAATTGC CTATCGTAAA 2400

TTCACATCAG CAAGTGATGT ATGGAGCTAT GGAATCGTTA TGTGGGAAGT 2450

GATGTCGTAC GGGGAGAGGC CCTATTGGGA TATGTCCAAT CAAGATGTGA 2500

TTAAAGCCAT TGAGGAAGGC TATCGGTTAC CCCCTCCAAT GGACTGCCCC 2550

ATTGCGCTCC ACCAGCTGAT GCTAGACTGC TGGCAGAAGG AGAGGAGCGA 2600

CAGGCCTAAA TTTGGGCAGA TTGTCAACAT GTTGGACAAA CTCATCCGCA 2650

ACCCCAACAG CTTGAAGAGG ACAGGGACGG AGAGCTCCAG ACCTAACACT 2700

GCCTTGTTGG ATCCAAGCTC CCCTGAATTC TCTGCTGTGG TATCAGTGGG 2750

CGATTGGCTC CAGGCCATTA AAATGGACCG GTATAAGGAT AACTTCACAG 2800

CTGCTGGTTA TACCACACTA GAGGCTGTGG TGCACGTGAA CCAGGAGGAC 2850

CTGGCAAGAA TTGGTATCAC AGCCATCACA CACCAGAATA AGATTTTGAG 2900

CAGTGTCCAG GCAATGCGAA CCCAAATGCA GCAGATGCAC GGCAGAATGG 2950

TTCCCGTCTG AGCCAGTACT GAATAAACTC AAAACTCTTG AAATTAGTTT 3000

ACCTCATCCA TGCACTTTAA TTGAAGAACT GCACTTTTTT TACTTCGTCT 3050

TCGCCCTCTG AAATTAAAGA AATGAAAAAA AAAAAACAAT ATCTGCAGCG 3100

TTGCTTGGTG CACAGATTGC TGAAACTGTG GGGCTTACAG AAATGACTGC 3150

CGGTCATTTG AATGAGACCT GGAACAAATC GTTTCTCAGA AGTACTTTTC 3200

TGTTCATCAC CAGTCTGTAA AATACATGTA CCTATAGAAA TAGAACACTG 3250

CCTCTGAGTT TTGATGCTGT ATTTGCTGCC AGACACTGAG CTTCTGAGAC 3300

ATCCCTGATT CTCTCTCCAT TTGGAATTAC AACGGTCGAC GAGCTCGA 3348

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3348 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TACCGACCCT AAAAGATAAA GCGGGATAAA AGCACAGAGA AGCCCTAAAC 50

GCTGCGACAG TGTCCAAGGT CCCATATGGG GCGCTTACTT CAATGGAATA 100

ACCTAAGGTC TAGACAAGTC CCTCTTGAAC CCACCTATCG TTCGGGAGAC 150

CTTCCTCCCA CCCTCCTTCA CTCATAGTAC CTACTTTTTT TATGTGGTTA 200

GGCTTGGATG GTTCACACGT TACACTACCT TGGGTCGGTC TTATTGACCG 250

ATGCTTGACT AACCTAGTGG GCTCTTCCCC GAGTCTCCCA CATATAACTC 300

TAATTTAAGT GGAACTCCCT GACGTTATCA GAAGGCCCGC AGTACCCCTG 350

AACGTTCCTC TGCAAATTGG ACATGATGAT ACTTAGTCTG TTGCTGTTTC 400

TCGCAAAGTA GTCTCTCTTG GTCAAACAGT TTTAACTGTG GTAACGACGA 450

CTACTCTCGA AGTGGGTTCA CCTGTAACCA CTGTCTTAGT ACTTCGACTT 500

GTGGCTCTAG GCCCTACATC CCGGTAATTC GTTTTTCCCC AAAATGGACC 550

GAAAAGTCCT ACACCCCCGG ACGTAGCGGG ACCATAGTCA GGCACACAAG 600

ATATTTTTCA CAGGTGAGTG TCAGGCGTTA GACCGGGTCA AAGGACTGTG 650

GTAGTGTCCC CGACTATGCA GAAGGGACCA CCTTCAAGCT CCGAGGACAC 700

AGTTGTTGAG TCTTCTCTTT CTACACGGTT TTTACATGAC ACCCCGTCTA 750

CCACTTACCG ACCATGGGTA ACCGTTGACG GATACGTTGC GACCCGTACT 800

CCTCGCCTCG CCTCTTACGG TTCGAACGTT TTAACCTATA ATGTTCCGAG 850

AGAGGTGCCT ACGGTGGACA CGGTTCACGG GTGGGGTGTC GATGAGACAG 900

ACCCTTCCTC GGTGGAGCAC GTGGACACTG GCTCCGAAAA AGTCTCGACT 950

GTTGCTACGA CGGAGATACG GGACGTGGGC AGGTGGTAGA CGAGGGGACT 1000

TGAACTAAAG TTTACAGTTG CTCTGTAGAC ACTTGAACCT TACCTCATCG 1050

GGAGTCTTAT GTCCACCGGC GGTCCTGTAA AGGATATTAC ACCATACGTT 1100

CTTTACACCT CGACCACTGG GGTCGTTCAC GGCTGGGACA CCTTCACCCC 1150

AGGTGATGTG GGGTGTCGTC TTACCGAACT TCTGGTGGTT TCCGAGGTAG 1200

TGACTGGAGG ATCGAGTATG GTTAATGTGG AAACTTTAGA CCCGACACTT 1250

ACCTCACAGG TTTATATTGG GATTGGGTCT GGTTAGTCAA AGACAGTGAC 1300

ACTGGTGGTT GGTTCGTCGT GGTAGTAGGT AACGAAACCA GGTCCGATTT 1350

CTTCAGTGTT CTATGTCACA CCGTGACCGA ACCGACCTTG GTCTAGCCGG 1400

GTTACCCCAT TAGGACCTTA TACTTCAGTT CATAATACTC TTCCTAGTCT 1450

TACTCGCTTC GATAGCATAT CAAGCCTGTC GACGGTCCTT GTGTCTATAG 1500

TTTCCGGACT TGGGAGAGTG AAGGATACAA AAGGTGCACG CTCGGTCCTG 1550

TCGTCGACCG ATACCTCTGA AGTCACTCGG GAACCTCCAA TGTTGGTTGT 1600

GTCACGGAAG GGCCTAGTAA CCTCTACCCC GATTGAGGTG TCAGGAAGAC 1650

CAGAGACAGA GCCCGTCACA CCACGACCAC CATTAAGAGT AACGTCGAAA 1700

ACAGTAGTCG GCCTCTGCCT CATTTATGTC ATTTCGGTTT GTTCTTCGCC 1750

TACTTCTCTT TGTAAACTTA GTTCCACATT CTTGTATACA CCTGGGGAAA 1800

TGCATGCTTC TAGGGTTGGT TCGTCACGCT CTCAAACGGT TTCTTTAACT 1850

GCGTAGGACG TAATTCTAAC TTTTTCAATA TCCTCAACCA CTTAAACCAC 1900

TCCATACGTC ACCCGCAGAG TTTCACGGAC CGTTCTCTCT CTAGACACAC 1950

CGATAGTTCT GAGACTTTCG ACCAATATGT CTGTTTGTCT CCTCTCTGAA 2000

GGACTCACTC CGGTCGTAGT ACCCTGTCAA ACTGGTAGGC TTGTAGTAAG 2050

TGAACCTTCC GCACCAGTGA TTTACATTTG GTCATTACTA GTATTGTCTC 2100

ATGTACCTCT TACCGAGGAA CCTACGTAAG GAGTCCTTTT TACTACCGTC 2150

TAAATGTCAG TAAGTCGACC ACCCGTACGA AGCACCGTAA CCCAGACCCT 2200

ACTTCATAAA TAGACTATAC TCGATACACG TAGCACTAGA CCGGCGTGCC 2250

TTGTAGGACC ACTTGTCGTT GAACCAGACG TTTCACAGAC TAAAACCGTA 2300

CAGGGCTCAC GAACTCCTAC TAGGCCTTCG TCGAATGTGG TGGTCCCCAC 2350

CGTTCTAAGG ATAGGCCACC TGACGCGGTC TTCGTTAACG GATAGCATTT 2400

AAGTGTAGTC GTTCACTACA TACCTCGATA CCTTAGCAAT ACACCCTTCA 2450

CTACAGCATG CCCCTCTCCG GGATAACCCT ATACAGGTTA GTTCTACACT 2500

AATTTCGGTA ACTCCTTCCG ATAGCCAATG GGGGAGGTTA CCTGACGGGG 2550

TAACGCGAGG TGGTCGACTA CGATCTGACG ACCGTCTTCC TCTCCTCGCT 2600

GTCCGGATTT AAACCCGTCT AACAGTTGTA CAACCTGTTT GAGTAGGCGT 2650

TGGGGTTGTC GAACTTCTCC TGTCCCTGCC TCTCGAGGTC TGGATTGTGA 2700

CGGAACAACC TAGGTTCGAG GGGACTTAAG AGACGACACC ATAGTCACCC 2750

GCTAACCGAG GTCCGGTAAT TTTACCTGGC CATATTCCTA TTGAAGTGTC 2800

GACGACCAAT ATGGTGTGAT CTCCGACACC ACGTGCACTT GGTCCTCCTG 2850

GACCGTTCTT AACCATAGTG TCGGTAGTGT GTGGTCTTAT TCTAAAACTC 2900

GTCACAGGTC CGTTACGCTT GGGTTTACGT CGTCTACGTG CCGTCTTACC 2950

AAGGGCAGAC TCGGTCATGA CTTATTTGAG TTTTGAGAAC TTTAATCAAA 3000

TGGAGTAGGT ACGTGAAATT AACTTCTTGA CGTGAAAAAA ATGAAGCAGA 3050

AGCGGGAGAC TTTAATTTCT TTACTTTTTT TTTTTTGTTA TAGACGTCGC 3100

AACGAACCAC GTGTCTAACG ACTTTGACAC CCCGAATGTC TTTACTGACG 3150

GCCAGTAAAC TTACTCTGGA CCTTGTTTAG CAAAGAGTCT TCATGAAAAG 3200

ACAAGTAGTG GTCAGACATT TTATGTACAT GGATATCTTT ATCTTGTGAC 3250

GGAGACTCAA AACTACGACA TAAACGACGG TCTGTGACTC GAAGACTCTG 3300

TAGGGACTAA GAGAGAGGTA AACCTTAATG TTGCCAGCTG CTCGAGCT 3348

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1104 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly
1 5 10 15

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Ile Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu
                20                  25                  30

Val Thr Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp
                35                  40                  45

Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met
                50                  55                  60

Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val
                65                  70                  75

Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr
                80                  85                  90

Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe Thr Leu
                95                 100                 105

Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys Glu
               110                 115                 120

Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg
               125                 130                 135

Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala
               140                 145                 150

Asp Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys
               155                 160                 165

Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly
               170                 175                 180

Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val
               185                 190                 195

Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn
               200                 205                 210

Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser
               215                 220                 225

Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
               230                 235                 240

Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val
               245                 250                 255

Pro Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser
               260                 265                 270

Gly Glu Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser
               275                 280                 285

Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val
               290                 295                 300
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Trp Glu Gly Ala Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg
                305                 310                 315

Ala Asp Asn Asp Ala Ala Ser Met Pro Cys Thr Arg Pro Pro Ser
                320                 325                 330

Ala Pro Leu Asn Leu Ile Ser Asn Val Asn Glu Thr Ser Val Asn
                335                 340                 345

Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly Arg Gln Asp Ile
                350                 355                 360

Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly Asp Pro Ser
                365                 370                 375

Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro Gln Gln
                380                 385                 390

Asn Gly Leu Lys Thr Thr Lys Gly Ser Ile Thr Asp Leu Leu Ala
                395                 400                 405

His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser
                410                 415                 420

Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr
                425                 430                 435

Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys
                440                 445                 450

Glu Val Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro Asp
                455                 460                 465

Arg Pro Asn Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu
                470                 475                 480

Lys Asp Gln Asn Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala
                485                 490                 495

Arg Asn Thr Asp Ile Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val
                500                 505                 510

Phe His Val Arg Ala Arg Thr Ala Ala Gly Tyr Gly Asp Phe Ser
                515                 520                 525

Glu Pro Leu Glu Val Thr Thr Asn Thr Val Pro Ser Arg Ile Ile
                530                 535                 540

Gly Asp Gly Ala Asn Ser Thr Val Leu Leu Val Ser Val Ser Gly
                545                 550                 555

Ser Val Val Leu Val Val Ile Leu Ile Ala Ala Phe Val Ile Ser
                560                 565                 570

Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Gln Glu Ala Asp Glu
                575                 580                 585
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Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro Phe
                590                 595                 600

Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu
                605                 610                 615

Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly
                620                 625                 630

Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys
                635                 640                 645

Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr
                650                 655                 660

Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly
                665                 670                 675

Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val Val Thr
                680                 685                 690

Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn Gly
                695                 700                 705

Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val
                710                 715                 720

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys
                725                 730                 735

Tyr Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg
                740                 745                 750

Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe
                755                 760                 765

Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr
                770                 775                 780

Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala
                785                 790                 795

Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr
                800                 805                 810

Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr
                815                 820                 825

Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala Ile Glu Glu Gly
                830                 835                 840

Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala Leu His Gln
                845                 850                 855

Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg Pro Lys
                860                 865                 870
```

Phe Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro
875 880 885

Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr
890 895 900

Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser
905 910 915

Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp
920 925 930

Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val His
935 940 945

Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr
950 955 960

His Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln
965 970 975

Met Gln Gln Met His Gly Arg Met Val Pro Val Ala Ser Thr Glu
980 985 990

Thr Gln Asn Ser Asn Phe Thr Ser Ser Met His Phe Asn Arg Thr
995 1000 1005

Ala Leu Phe Leu Leu Arg Leu Arg Pro Leu Lys Leu Lys Lys Lys
1010 1015 1020

Lys Lys Asn Asn Ile Cys Ser Val Ala Trp Cys Thr Asp Cys Asn
1025 1030 1035

Cys Gly Ala Tyr Arg Asn Asp Cys Arg Ser Phe Glu Asp Leu Glu
1040 1045 1050

Gln Ile Val Ser Gln Lys Tyr Phe Ser Val His His Gln Ser Val
1055 1060 1065

Lys Tyr Met Tyr Leu Lys Asn Thr Ala Ser Glu Phe Cys Cys Ile
1070 1075 1080

Cys Cys Gln Thr Leu Ser Phe Asp Ile Pro Asp Ser Leu Ser Ile
1085 1090 1095

Trp Asn Tyr Asn Gly Arg Arg Ala Arg
1100 1104

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCGGATCCAC ACGNGACTCT TGGC 24

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TCGGATCCAC TCAGNGACTC TTNGCNGC 28

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCGAATTCC AGATAAGCGT ACCAGCACAG TC 32

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CTCGAATTCC AGATATCCGT ACCATAACAG TC 32

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Met Asp Tyr Lys Asp Asp Asp Asp Lys Lys Leu Ala Met
1 5 10 13

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CCGGATATCA TGGACTACAA GGACGACGAT GACAAGAAGC TTGCCATGGA 50

GCTC 54

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

AGGCTGCTGG AGGAAAAGTC TG 22

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GGAGGGTGAC CTCCATGCTG CCCTTATCCT CG 32

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9108 bases

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT 50

TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC 100

TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG 150

ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA 200

TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC TTGGCAGTAC 250

ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT 300

AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC 350

TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC 400

GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA 450

TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA 500

AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC 550

AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT 600

TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT 650

CCATAGAAGA CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA 700

TTGGAACGCG GATTCCCCGT GCCAAGAGTG ACGTAAGTAC CGCCTATAGA 750

GTCTATAGGC CCACCCCCTT GGCTTCGTTA GAACGCGGCT ACAATTAATA 800

CATAACCTTA TGTATCATAC ACATACGATT TAGGTGACAC TATAGAATAA 850

CATCCACTTT GCCTTTCTCT CCACAGGTGT CCACTCCCAG GTCCAACTGC 900

ACCTCGGTTC TATCGATTGA ATTCGCGGCC GCTCGGGTCG GACCCACGCG 950

CAGCGGCCGG AGATGCAGCG GGGCGCCGCG CTGTGCCTGC GACTGTGGCT 1000

CTGCCTGGGA CTCCTGGACG GCCTGGTGAG TGGCTACTCC ATGACCCCCC 1050

CGACCTTGAA CATCACGGAG GAGTCACACG TCATCGACAC CGGTGACAGC 1100

CTGTCCATCT CCTGCAGGGG ACAGCACCCC CTCGAGTGGG CTTGGCCAGG 1150

AGCTCAGGAG GCGCCAGCCA CCGGAGACAA GGACAGCGAG GACACGGGGG 1200

TGGTGCGAGA CTGCGAGGGC ACAGACGCCA GGCCCTACTG CAAGGTGTTG 1250

CTGCTGCACG AGGTACATGC CAACGACACA GGCAGCTACG TCTGCTACTA 1300

CAAGTACATC AAGGCACGCA TCGAGGGCAC CACGGCCGCC AGCTCCTACG 1350

TGTTCGTGAG AGACTTTGAG CAGCCATTCA TCAACAAGCC TGACACGCTC 1400

TTGGTCAACA GGAAGGACGC CATGTGGGTG CCCTGTCTGG TGTCCATCCC 1450

CGGCCTCAAT GTCACGCTGC GCTCGCAAAG CTCGGTGCTG TGGCCAGACG 1500

GGCAGGAGGT GGTGTGGGAT GACCGGCGGG GCATGCTCGT GTCCACGCCA 1550

CTGCTGCACG ATGCCCTGTA CCTGCAGTGC GAGACCACCT GGGGAGACCA 1600

GGACTTCCTT TCCAACCCCT TCCTGGTGCA CATCACAGGC AACGAGCTCT 1650

ATGACATCCA GCTGTTGCCC AGGAAGTCGC TGGAGCTGCT GGTAGGGGAG 1700

AAGCTGGTCC TGAACTGCAC CGTGTGGGCT GAGTTTAACT CAGGTGTCAC 1750

CTTTGACTGG GACTACCCAG GGAAGCAGGC AGAGCGGGGT AAGTGGGTGC 1800

CCGAGCGACG CTCCCAGCAG ACCCACACAG AACTCTCCAG CATCCTGACC 1850

ATCCACAACG TCAGCCAGCA CGACCTGGGC TCGTATGTGT GCAAGGCCAA 1900

CAACGGCATC CAGCGATTTC GGGAGAGCAC CGAGGTCATT GTGCATGAAA 1950

ATCCCTTCAT CAGCGTCGAG TGGCTCAAAG GACCCATCCT GGAGGCCACG 2000

GCAGGAGACG AGCTGGTGAA GCTGCCCGTG AAGCTGGCAG CGTACCCCCC 2050

GCCCGAGTTC CAGTGGTACA AGGATGGAAA GGCACTGTCC GGGCGCCACA 2100

GTCCACATGC CCTGGTGCTC AAGGAGGTGA CAGAGGCCAG CACAGGCACC 2150

TACACCCTCG CCCTGTGGAA CTCCGCTGCT GGCCTGAGGC GCAACATCAG 2200

CCTGGAGCTG GTGGTGAATG TGCCCCCCCA GATACATGAG AAGGAGGCCT 2250

CCTCCCCCAG CATCTACTCG CGTCACAGCC GCCAGGCCCT CACCTGCACG 2300

GCCTACGGGG TGCCCCTGCC TCTCAGCATC CAGTGGCACT GGCGGCCCTG 2350

GACACCCTGC AAGATGTTTG CCCAGCGTAG TCTCCGGCGG CGGCAGCAGC 2400

AAGACCTCAT GCCACAGTGC CGTGACTGGA GGGCGGTGAC CACGCAGGAT 2450

GCCGTGAACC CCATCGAGAG CCTGGACACC TGGACCGAGT TTGTGGAGGG 2500

AAAGAATAAG ACTGTGAGCA AGCTGGTGAT CCAGAATGCC AACGTGTCTG 2550

CCATGTACAA GTGTGTGGTC TCCAACAAGG TGGGCCAGGA TGAGCGGCTC 2600

ATCTACTTCT ATGTGACCAC CATCCCCGAC GGCTTCACCA TCGAATCCAA 2650

GCCATCCGAG GAGCTACTAG AGGGCCAGCC GGTGCTCCTG AGCTGCCAAG 2700

CCGACAGCTA CAAGTACGAG CATCTGCGCT GGTACCGCCT CAACCTGTCC 2750

ACGCTGCACG ATGCGCACGG GAACCCGCTT CTGCTCGACT GCAAGAACGT 2800

GCATCTGTTC GCCACCCCTC TGGCCGCCAG CCTGGAGGAG GTGGCACCTG 2850

GGGCGCGCCA CGCCACGCTC AGCCTGAGTA TCCCCCGCGT CGCGCCCGAG 2900

CACGAGGGCC ACTATGTGTG CGAAGTGCAA GACCGGCGCA GCCATGACAA 2950

GCACTGCCAC AAGAAGTACC TGTCGGTGCA GGCCCTGGAA GCCCCTCGGC 3000

TCACGCAGAA CTTGACCGAC CTCCTGGTGA ACGTGAGCGA CTCGCTGGAG 3050

ATGCAGTGCT TGGTGGCCGG AGCGCACGCG CCCAGCATCG TGTGGTACAA 3100

AGACGAGAGG CTGCTGGAGG AAAAGTCTGG AGTCGACTTG GCGGACTCCA 3150

ACCAGAAGCT GAGCATCCAG CGCGTGCGCG AGGAGGATGC GGGACGCTAT 3200

CTGTGCAGCG TGTGCAACGC CAAGGGCTGC GTCAACTCCT CCGCCAGCGT 3250

GGCCGTGGAA GGCTCCGAGG ATAAGGGCAG CATGGAGATC GTGATCCTTG 3300

TCGGTACCGG CGTCATCGCT GTCTTCTTCT GGGTCCTCCT CCTCCTCATC 3350

TTCTGTAACA TGAGGAGGCC GGCCCACGCA GACATCAAGA CGGGCTACCT 3400

GTCCATCATC ATGGACCCCG GGGAGGTGCC TCTGGAGGAG CAATGCGAAT 3450

ACCTGTCCTA CGATGCCAGC CAGTGGGAAT TCCCCCGAGA GCGGCTGCAC 3500

CTGGGGAGAG TGCTCGGCTA CGGCGCCTTC GGGAAGGTGG TGGAAGCCTC 3550

CGCTTTCGGC ATCCACAAGG GCAGCAGCTG TGACACCGTG GCCGTGAAAA 3600

TGCTGAAAGA GGGCGCCACG GCCAGCGAGC ACCGCGCGCT GATGTCGGAG 3650

CTCAAGATCC TCATTCACAT CGGCAACCAC CTCAACGTGG TCAACCTCCT 3700

CGGGGCGTGC ACCAAGCCGC AGGGCCCCCT CATGGTGATC GTGGAGTTCT 3750

GCAAGTACGG CAACCTCTCC AACTTCCTGC GCGCCAAGCG GGACGCCTTC 3800

AGCCCCTGCG CGGAGAAGTC TCCCGAGCAG CGCGGACGCT TCCGCGCCAT 3850

GGTGGAGCTC GCCAGGCTGG ATCGGAGGCG GCCGGGGAGC AGCGACAGGG 3900

TCCTCTTCGC GCGGTTCTCG AAGACCGAGG GCGGAGCGAG GCGGGCTTCT 3950

CCAGACCAAG AAGCTGAGGA CCTGTGGCTG AGCCCGCTGA CCATGGAAGA 4000

TCTTGTCTGC TACAGCTTCC AGGTGGCCAG AGGGATGGAG TTCCTGGCTT 4050

CCCGAAAGTG CATCCACAGA GACCTGGCTG CTCGGAACAT TCTGCTGTCG 4100

GAAAGCGACG TGGTGAAGAT CTGTGACTTT GGCCTTGCCC GGGACATCTA 4150

CAAAGACCCT GACTACGTCC GCAAGGGCAG TGCCCGGCTG CCCCTGAAGT 4200

GGATGGCCCC TGAAAGCATC TTCGACAAGG TGTACACCAC GCAGAGTGAC 4250

GTGTGGTCCT TTGGGGTGCT TCTCTGGGAG ATCTTCTCTC TGGGGGCCTC 4300

CCCGTACCCT GGGGTGCAGA TCAATGAGGA GTTCTGCCAG CGGCTGAGAG 4350

ACGGCACAAG GATGAGGGCC CCGGAGCTGG CCACTCCCGC CATACGCCGC 4400

ATCATGCTGA ACTGCTGGTC CGGAGACCCC AAGGCGAGAC CTGCATTCTC 4450

GGAGCTGGTG GAGATCCTGG GGGACCTGCT CCAGGGCAGG GGCCTGCAAG 4500

AGGAAGAGGA GGTCTGCATG GCCCCGCGCA GCTCTCAGAG CTCAGAAGAG 4550

GGCAGCTTCT CGCAGGTGTC CACCATGGCC CTACACATCG CCCAGGCTGA 4600

CGCTGAGGAC AGCCCGCCAA GCCTGCAGCG CCACAGCCTG GCCGCCAGGT 4650

ATTACAACTG GGTGTCCTTT CCCGGGTGCC TGGCCAGAGG GGCTGAGACC 4700

CGTGGTTCCT CCAGGATGAA GACATTTGAG GAATTCCCCA TGACCCCAAC 4750

GACCTACAAA GGCTCTGTGG ACAACCAGAC AGACAGTGGG ATGGTGCTGG 4800

CCTCGGAGGA GTTTGAGCAG ATAGAGAGCA GGCATAGACA AGAAAGCGGC 4850

TTCAGGTAGC TGAAGCAGAG AGAGAGAAGG CAGCATACGT CAGCATTTTC 4900

TTCTCTGCAC TTATAAGAAA GATCAAAGAC TTTAAGACTT TCGCTATTTC 4950

TTCTGCTATC TACTACAAAC TTCAAAGAGG AACCAGGAGG CCAAGAGGAG 5000

CATGAAAGTG GACAAGGAGT GTGACCACTG AAGCACCACA GGGAGGGGTT 5050

AGGCCTCCGG ATGACTGCGG GCAGGCCTGG ATAATATCCA GCCTCCCACA 5100

AGAAGCTGGT GGAGCAGAGT GTTCCCTGAC TCCTCCAAGG AAAGGGAGAC 5150

GCCCTTTCAT GGTCTGCTGA GTAACAGGTG CCTTCCCAGA CACTGGCGTT 5200

ACTGCTTGAC CAAAGAGCCC TCAAGCGGCC CTTATGCCAG CGTGACAGAG 5250

GGCTCACCTC TTGCCTTCTA GGTCACTTCT CACAATGTCC CTTCAGCACC 5300

TGACCCTGTG CCCGCCAGTT ATTCCTTGGT AATATGAGTA ATACATCAAA 5350

GAGTAGTGCG GCCGCGAATT CCCCGGGGAT CCTCTAGAGT CGACCTGCAG 5400

AAGCTTGGCC GCCATGGCCC AACTTGTTTA TTGCAGCTTA TAATGGTTAC 5450

AAATAAAGCA ATAGCATCAC AAATTTCACA AATAAAGCAT TTTTTTCACT 5500

GCATTCTAGT TGTGGTTTGT CCAAACTCAT CAATGTATCT TATCATGTCT 5550

GGATCGGGAA TTAATTCGGC GCAGCACCAT GGCCTGAAAT AACCTCTGAA 5600

AGAGGAACTT GGTTAGGTAC CTTCTGAGGC GGAAAGAACC AGCTGTGGAA 5650

TGTGTGTCAG TTAGGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA 5700

GTATGCAAAG CATGCATCTC AATTAGTCAG CAACCAGGTG TGGAAAGTCC 5750

CCAGGCTCCC CAGCAGGCAG AAGTATGCAA AGCATGCATC TCAATTAGTC 5800

AGCAACCATA GTCCCGCCCC TAACTCCGCC CATCCCGCCC CTAACTCCGC 5850

CCAGTTCCGC CCATTCTCCG CCCCATGGCT GACTAATTTT TTTTATTTAT 5900

GCAGAGGCCG AGGCCGCCTC GGCCTCTGAG CTATTCCAGA AGTAGTGAGG 5950

AGGCTTTTTT GGAGGCCTAG GCTTTTGCAA AAAGCTGTTA ACAGCTTGGC 6000

ACTGGCCGTC GTTTTACAAC GTCGTGACTG GGAAAACCCT GGCGTTACCC 6050

AACTTAATCG CCTTGCAGCA CATCCCCCTT TCGCCAGCTG GCGTAATAGC 6100

GAAGAGGCCC GCACCGATCG CCCTTCCCAA CAGTTGCGCA GCCTGAATGG 6150

CGAATGGCGC CTGATGCGGT ATTTTCTCCT TACGCATCTG TGCGGTATTT 6200

CACACCGCAT ACGTCAAAGC AACCATAGTA CGCGCCCTGT AGCGGCGCAT 6250

TAAGCGCGGC GGGTGTGGTG GTTACGCGCA GCGTGACCGC TACACTTGCC 6300

AGCGCCCTAG CGCCCGCTCC TTTCGCTTTC TTCCCTTCCT TTCTCGCCAC 6350

GTTCGCCGGC TTTCCCCGTC AAGCTCTAAA TCGGGGGCTC CCTTTAGGGT 6400

TCCGATTTAG TGCTTTACGG CACCTCGACC CCAAAAAACT TGATTTGGGT 6450

GATGGTTCAC GTAGTGGGCC ATCGCCCTGA TAGACGGTTT TTCGCCCTTT 6500

GACGTTGGAG TCCACGTTCT TTAATAGTGG ACTCTTGTTC CAAACTGGAA 6550

CAACACTCAA CCCTATCTCG GGCTATTCTT TTGATTTATA AGGGATTTTG 6600

CCGATTTCGG CCTATTGGTT AAAAAATGAG CTGATTTAAC AAAAATTTAA 6650

CGCGAATTTT AACAAAATAT TAACGTTTAC AATTTTATGG TGCACTCTCA 6700

GTACAATCTG CTCTGATGCC GCATAGTTAA GCCAGCCCCG ACACCCGCCA 6750

ACACCCGCTG ACGCGCCCTG ACGGGCTTGT CTGCTCCCGG CATCCGCTTA 6800

CAGACAAGCT GTGACCGTCT CCGGGAGCTG CATGTGTCAG AGGTTTTCAC 6850

CGTCATCACC GAAACGCGCG AGACGAAAGG GCCTCGTGAT ACGCCTATTT 6900

TTATAGGTTA ATGTCATGAT AATAATGGTT TCTTAGACGT CAGGTGGCAC 6950

TTTTCGGGGA AATGTGCGCG GAACCCCTAT TTGTTTATTT TTCTAAATAC 7000

ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA AATGCTTCAA 7050

TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC GTGTCGCCCT 7100

TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT CACCCAGAAA 7150

CGCTGGTGAA AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT 7200

TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC 7250

CGAAGAACGT TTTCCAATGA TGAGCACTTT TAAAGTTCTG CTATGTGGCG 7300

CGGTATTATC CCGTATTGAC GCCGGGCAAG AGCAACTCGG TCGCCGCATA 7350

CACTATTCTC AGAATGACTT GGTTGAGTAC TCACCAGTCA CAGAAAAGCA 7400

TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT GCCATAACCA 7450

TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT CGGAGGACCG 7500

AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG TAACTCGCCT 7550

TGATCGTTGG GAACCGGAGC TGAATGAAGC CATACCAAAC GACGAGCGTG 7600

ACACCACGAT GCCTGTAGCA ATGGCAACAA CGTTGCGCAA ACTATTAACT 7650

GGCGAACTAC TTACTCTAGC TTCCCGGCAA CAATTAATAG ACTGGATGGA 7700

GGCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT CCGGCTGGCT 7750

GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC TCGCGGTATC 7800

ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCGTATCG TAGTTATCTA 7850

CACGACGGGG AGTCAGGCAA CTATGGATGA ACGAAATAGA CAGATCGCTG 7900

AGATAGGTGC CTCACTGATT AAGCATTGGT AACTGTCAGA CCAAGTTTAC 7950

TCATATATAC TTTAGATTGA TTTAAAACTT CATTTTTAAT TTAAAAGGAT 8000

CTAGGTGAAG ATCCTTTTTG ATAATCTCAT GACCAAAATC CCTTAACGTG 8050

AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT 8100

TCTTGAGATC CTTTTTTTCT GCGCGTAATC TGCTGCTTGC AAACAAAAAA 8150

ACCACCGCTA CCAGCGGTGG TTTGTTTGCC GGATCAAGAG CTACCAACTC 8200

TTTTTCCGAA GGTAACTGGC TTCAGCAGAG CGCAGATACC AAATACTGTT 8250

CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT CTGTAGCACC 8300

GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT GCTGCCAGTG 8350

GCGATAAGTC GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT 8400

AAGGCGCAGC GGTCGGGCTG AACGGGGGGT TCGTGCACAC AGCCCAGCTT 8450

GGAGCGAACG ACCTACACCG AACTGAGATA CCTACAGCGT GAGCTATGAG 8500

AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG CGGACAGGTA TCCGGTAAGC 8550

GGCAGGGTCG GAACAGGAGA GCGCACGAGG GAGCTTCCAG GGGGAAACGC 8600

CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA CTTGAGCGTC 8650

GATTTTTGTG ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC 8700

AACGCGGCCT TTTTACGGTT CCTGGCCTTT TGCTGGCCTT TTGCTCACAT 8750

GTTCTTTCCT GCGTTATCCC CTGATTCTGT GGATAACCGT ATTACCGCCT 8800

TTGAGTGAGC TGATACCGCT CGCCGCAGCC GAACGACCGA GCGCAGCGAG 8850

TCAGTGAGCG AGGAAGCGGA AGAGCGCCCA ATACGCAAAC CGCCTCTCCC 8900

CGCGCGTTGG CCGATTCATT AATGCAGCTG GCACGACAGG TTTCCCGACT 8950

GGAAAGCGGG CAGTGAGCGC AACGCAATTA ATGTGAGTTA GCTCACTCAT 9000

TAGGCACCCC AGGCTTTACA CTTTATGCTT CCGGCTCGTA TGTTGTGTGG 9050

AATTGTGAGC GGATAACAAT TTCACACAGG AAACAGCTAT GACATGATTA 9100

CGAATTAA 9108

The invention claimed is:

1. An agonist antibody which activates the kinase domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
   a) SAL-S1;
   b) HpTK 5; and
   c) bpTK 7.
2. The antibody of claim 1 comprising a monoclonal antibody.
3. The antibody of claim 1 wherein the pTK is HpTK5.
4. The antibody of claim 3 having the biological characteristics of the antibody produced by the hybridoma cell line deposited under American Type Culture Collection Accession No. ATCC HB 11,583.
5. The antibody of claim 1 wherein the pTK is SAL-S1.
6. A pharmaceutical composition comprising the antibody of claim 1 in an amount effective in activating the kinase domain of the receptor protein tyrosine kinase (pTK), and a pharmaceutically acceptable carrier.
7. A method for activating the kinase domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
   a) SAL-S1;
   b) HpTK 5; and
   c) bpTK 7, comprising contacting the pTK with an effective amount of an agonist antibody thereto.
8. A chimeric protein comprising a fusion of the extracellular domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:
   a) SAL-S1;
   b) HpTK 5; and
   c) bpTK 7, with an immunoglobulin constant domain sequence.
9. The chimeric protein of claim 8 wherein the pTK is HpTK5.
10. The chimeric protein of claim 8 wherein the pTK is Sal-S1.
11. The chimeric protein of claim 8 wherein the immunoglobulin constant domain sequence is that of an IgG immunoglobulin.
12. A nucleic acid encoding the chimeric protein of claim 8.

13. A replicable vector comprising the nucleic acid of claim 12.

14. A recombinant host cell comprising the nucleic acid of claim 12.

15. A method of using a nucleic acid molecule encoding a chimeric protein comprising a fusion of the extracellular domain of a receptor protein tyrosine kinase (pTK) selected from the group consisting of:

a) SAL-S1;

b) HpTK 5; and

c) bpTK 7, with an immunoglobulin constant domain sequence, to effect the production of the chimeric protein comprising culturing the host cell of claim 14.

FIG. 1A

```
GGATCCTGTG CATCAGTGAC TTAGGGCTAG GAACATTCTG CTGTCGGAAA GCGACGTGGT      60

GAAGATCTGT GACTTTGGCC TTGCCCGGGA CATCTACAAA GACCCCAGCT ACGTCCGCAA     120

GCATGCCCGG CTGCCCCTGA AGTGGATGGC GCCAGAATTC                        160
```

FIG. 1B

```
Asp Pro Val His Gln Xaa Leu Arg Ala Arg Asn Ile Leu Leu Ser Glu
 1               5                  10                  15

Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr
            20                  25                  30

Lys Asp Pro Ser Tyr Val Arg Lys His Ala Arg Leu Pro Leu Lys Trp
        35                  40                  45

Met Ala Pro Glu Phe
    50
```

FIG. 2A

```
GGATCCATTC ACAGAGACCT AGCAGCACGC AACATCCTGG TCTCAGAGGA CCTGGTAACC    60

AAGGTCAGCG ACTTTGGCCT GGCCAAAGCC GAGCGGAAGG GGCTAGACTC AAGCCGGCTG   120

CCCGTCAAAT GGATGGCTCC CGAATTC                                       147
```

FIG. 2B

```
Gly Ser Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ser Glu
 1               5                  10                  15

Asp Leu Val Thr Lys Val Ser Asp Phe Gly Leu Ala Lys Ala Glu Arg
            20                  25                  30

Lys Gly Leu Asp Ser Ser Arg Leu Pro Val Lys Trp Met Ala Pro Glu
        35                  40                  45

Phe
```

FIG. 3A

```
GTT GGA ATT CCT TCC GGC GCC ATC CAT TTC ACC GGC AGC TTT ATT TCG          48
Val Gly Ile Pro Ser Gly Ala Ile His Phe Thr Gly Ser Phe Ile Ser
  1               5                  10                  15

TGT CTA GAT TCA TAG ATG TCT TCA TTA TCT ACC TTA AAA ACT CTG GCA          96
Cys Leu Asp Ser     Met Ser Ser Leu Ser Thr Leu Lys Thr Leu Ala
            20                  25                  30

AGT CCA AAA TCT GCT ACT TTG TAG ATA TTA TGT TCA CCA ACG AGG ACA         144
Ser Pro Lys Ser Ala Thr Leu     Ile Leu Cys Ser Pro Thr Arg Thr
            35                  40                  45

TTCCT                                                                   149
Phe
```

FIG. 3B

```
GTG CAC AGG GAT CTC GCG GCT CGG AAC ATC CTC GTC GGG GAA AAC ACC          48
Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn Thr
  1               5                  10                  15

CTC TCG AAA GTT GGG GAC TTC GGG TTA GCC AGG CTT ATC AAG GAG GAC          96
Leu Ser Lys Val Gly Asp Phe Gly Leu Ala Arg Leu Ile Lys Glu Asp
            20                  25                  30

GTC TAC CTC TCC CAT GAC CAC AAT ATC CCC TAC AAA TGG ATG GCC CCT         144
Val Tyr Leu Ser His Asp His Asn Ile Pro Tyr Lys Trp Met Ala Pro
        35                  40                  45

GAG GGA A                                                               151
Glu Gly
    50
```

FIG. 3C

```
GTT CAC CGA GAT CTC AAG TCC AAC AAC ATT TTG CTG CTG CAG CCC ATT          48
Val His Arg Asp Leu Lys Ser Asn Asn Ile Leu Leu Gln Pro Ile
  1               5                  10                  15

GAG AGT GAC GAC ATG GAG CAC AAG ACC CTG AAG ATC ACC GAC TTT GGC          96
Glu Ser Asp Asp Met Glu His Lys Thr Leu Lys Ile Thr Asp Phe Gly
            20                  25                  30

CTG GCC CGA GAG TGG CAC AAA ACC ACA CAA ATG AGT GCC GC                  137
Leu Ala Arg Glu Trp His Lys Thr Thr Gln Met Ser Ala
        35                  40                  45
```

FIG. 3D

```
GTC AAT CGT GAC CTC GCC GCC CGA AAT GTG TTG CTA GTT ACC CAA CAT          48
Val Asn Arg Asp Leu Ala Ala Arg Asn Val Leu Leu Val Thr Gln His
  1               5                  10                  15

TAC GCC AAG ATC AGT GAT TTC GGA CTT TCC AAA GCA CTG CGT GCT GAT          96
Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg Ala Asp
            20                  25                  30

GAA AAC TAC TAC AAG GCC CAG ACC CAT GGA AAG TGG CCT GTC AAG TGG         144
Glu Asn Tyr Tyr Lys Ala Gln Thr His Gly Lys Trp Pro Val Lys Trp
        35                  40                  45

TAC GCT CCG GAA TGC ATC AAC TAC TAC AAG TTC TCC AGC AAA AGC GAT         192
Tyr Ala Pro Glu Cys Ile Asn Tyr Tyr Lys Phe Ser Ser Lys Ser Asp
    50                  55                  60

GTC TGG TCC TTT GGA ATT C                                               211
Val Trp Ser Phe Gly Ile
65                  70
```

FIG. 4A

```
TTCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT TACGGGGTCA    60
TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCGCCT   120
GGCTGACCGC CCAACGACCC CCGCCCATTG ACGTCAATAA TGACGTATGT TCCCATAGTA   180
ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC   240
TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT   300
AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG   360
TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC GGTTTTGGCA GTACATCAAT   420
GGGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC TCCACCCCAT TGACGTCAAT   480
GGGAGTTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC   540
CCATTGACGC AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT   600
TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT CCATAGAAGA   660
CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA TTGGAACGCG GATTCCCCGT   720
GCCAAGAGTG ACGTAAGTAC CGCCTATAGA GTCTATAGGC CCACTTGGCT TCGTTAGAAC   780
GCGGCTACAA TTAATACATA ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA   840
GAATAACATC CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT   900
CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT CGAGATCCAT   960
TGTGCTGGCG CGGATTCTTT ATCACTGATA AGTTGGTGGA CATATTATGT TTATCAGTGA  1020
```

FIG. 4B

```
TAAAGTGTCA AGCATGACAA AGTTGCAGCC GAATACAGTG ATCCGTGCCG CCCTAGACCT   1080
GTTGAACGAG GTCGGCGTAG ACGGTCTGAC GACACGCAAA CTGGCGGAAC GGTTGGGGGT   1140
TCAGCAGCCG GCGCTTTACT GGCACTTCAG GAACAAGCGG GCGCTGCTCG ACGCACTGGC   1200
CGAAGCCATG CTGGCGGAGA ATCATAGCAC TTCGGTGCCG AGAGCCGACG ACGACTGGCG   1260
CTCATTTCTG ACTGGGAATG CCCGCAGCTT CAGGCAGGCG CTGCTCGCCT ACCGCCAGCA   1320
CAATGGATCT CGAGGGATCT TCCATACCTA CCAGTTCTGC GCCTGCAGGT CGCGGCCGCA   1380
CTACTCTTTG ATGTATTACT CATATTACCA AGGAATAACT GGCGGGCACA GGGTCAGGTG   1440
CTGAAGGGAC ATTGTGAGAA GTGACCTAGA AGGCAAGAGG TGAGCCCTCT GTCACGCTGG   1500
CATAAGGGCC GCTTGAGGGC TCTTTGGTCA AGCAGTAACG CCAGTGTCTG GGAAGGCACC   1560
TGTTACTCAG CAGACCATGA AAGGGCGTCT CCCTTTCCTT GGAGCAGTCA GGGAACACTC   1620
TGCTCCACCA GCTTCTTGTG GGAGCCTGGA TATTATCCAG GCCTGCCCGC AGTCATCCGG   1680
AGGCCTAACC CCTCCCTGTG GTGCTTCAGT GGTCACACTC CTTGTCCACT TTCATGCTCC   1740
TCTTGGCCTC CTGGTTCCTC TTGGAAGTTT GTAGTAGATA GCAGAAGAAA TAGCGAAAGT   1800
CTTAAAGTCT TTGATCTTTC TTATAAGTGC AGAGAAGAAA TGCTGACGTA TGCTGCCTTC   1860
TCTCTCTCTG CTTCAGCTAC CTGAAGCCGC TTTCTTGTCT ATACCTGCTC TCTATCTGCT   1920
CACACTCCTC CGAGGCCAGC ACCATCCCAC TGTCTGTCTG GTTGTCCACA GAGCCTTTGT   1980
AGGTCGTTGG GGTCATGGGG AATTCCTCAA ATGTCTTCAT CCTGGAGGAA CCACGGGTCT   2040
```

FIG. 4C

```
CAGCCCCTCT GGCCAGGCAC CCGGGAAAGG ACACCCAGTT GTAATACCTG GCGGCCAGGC   2100
TGTGGCGCTG CAGGCTTGGC GGGCTGTCCT CAGCGTCAGC CTGGGCGATG TGTAGGGCCA   2160
TGGTGGACAC CTGCGAGAAG CTGCCCTCTT CTGAGCTCTG AGAGCTGCGC GGGGCCATGC   2220
AGACCTCCTC TTCCTCTTGC AGGCCCCTGC CCTGGAGCAG GTCCCCCAGG ATCTCCACCA   2280
GCTCCGAGAA TGCAGGTCTC GCCTTGGGGT CTCCGGACCA GCAGTTCAGC ATGATGCGGC   2340
GTATGGCGGG AGTGGCCAGC TCCGGGGCCC TCATCCTTGT GCCGTCTCTC AGCCGCTGGC   2400
AGAACTCCTC ATTGATCTGC ACCCCAGGGT ACGGGGAGGC CCCCAGAGAG AAGATCTCCC   2460
AGAGAAGCAC CCCAAAGGAC CACACGTCAC TCTGCGTGGT GTACACCTTG TCGAAGATGC   2520
TTTCAGGGGC CATCCACTTC AGGGGCAGCC GGGCACTGCC CTTGCGGACG TAGTCGGGGT   2580
CTTTGTAGAT GTCCCGGGCA AGGCCAAAGT CACAGATCTT CACCACGTCG CTTTCCGACA   2640
GCAGAATGTT CCGAGCAGCC AGGTCTCTGT GGATGCACTT TCGGGAAGCC AGGAACTCCA   2700
TCCCTCTGGC CACCTGGAAG CTGTAGCAGA CAAGATCTTC CATGGTCAGC GGGCTCAGCC   2760
ACAGGTCCTC AGCTTCTTGG TCTGGAGAAG CCCGCCTCGC TCCGCCCTCG GTCTTCGAGA   2820
ACCGCGCGAA GAGGACCCTG TCGCTGCTCC CCGGCCGCCT CCGATCCAGC CTGGCGAGCT   2880
CCACCATGGC GCGGAAGCGT CCGCGCTGCT CGGGAGACTT CTCCTGCGGA TGCACGAAGC   2940
TGGCTCGAGG GCGCCCAGTC GTCCGCCGCA GAGGCGCCTC CATTCCCCCG CCGCCCGCGG   3000
CGCCCCGCAG GCCGCCCGCT CACCGNGCAG GGGCTGCGGC CGCGACTCTA GAGTCGACCT   3060
```

FIG. 4D

```
GCAGAAGCTT GGCCGCCATG GCCCAACTTG TTTATTGCAG CTTATAATGG TTACAAATAA   3120
AGCAATAGCA TCACAAATTT CACAAATAAA GCATTTTTTT CACTGCATTC TAGTTGTGGT   3180
TTGTCCAAAC TCATCAATGT ATCTTATCAT GTCTGGATCG ATCGGGAATT AATTCGGCGC   3240
AGCACCATGG CCTGAAATAA CCTCTGAAAG AGGAACTTGG TTAGGTACCT TCTGAGGCGG   3300
AAAGAACCAG CTGTGGAATG TGTGTCAGTT AGGGTGTGGA AAGTCCCCAG GCTCCCCAGC   3360
AGGCAGAAGT ATGCAAAGCA TGCATCTCAA TTAGTCAGCA ACCAGGTGTG GAAAGTCCCC   3420
AGGCTCCCCA GCAGGCAGAA GTATGCAAAG CATGCATCTC AATTAGTCAG CAACCATAGT   3480
CCCGCCCCTA ACTCCGCCCA TCCCGCCCCT AACTCCGCCC AGTTCCGCCC ATTCTCCGCC   3540
CCATGGCTGA CTAATTTTTT TTATTTATGC AGAGGCCGAG GCCGCCTCGG CCTCTGAGCT   3600
ATTCCAGAAG TAGTGAGGAG GCTTTTTTGG AGGCCTAGGC TTTTGCAAAA AGCTGTTAAC   3660
AGCTTGGCAC TGGCCGTCGT TTTACAACGT CGTGACTGGG AAAACCCTGG CGTTACCCAA   3720
CTTAATCGCC TTGCAGCACA TCCCCCCTTC GCCAGCTGGC GTAATAGCGA AGAGGCCCGC   3780
ACCGATCGCC CTTCCCAACA GTTGCGTAGC CTGAATGGCG AATGGCGCCT GATGCGGTAT   3840
TTTCTCCTTA CGCATCTGTG CGGTATTTCA CACCGCATAC GTCAAAGCAA CCATAGTACG   3900
CGCCCTGTAG CGGCGCATTA AGCGCGGCGG GTGTGGTGGT TACGCGCAGC GTGACCGCTA   3960
CACTTGCCAG CGCCCTAGCG CCCGCTCCTT TCGCTTTCTT CCCTTCCTTT CTCGCCACGT   4020
TCGCCGGCTT TCCCCGTCAA GCTCTAAATC GGGGGCTCCC TTTAGGGTTC CGATTTAGTG   4080
```

FIG. 4E

```
CTTTACGGCA CCTCGACCCC AAAAAACTTG ATTTGGGTGA TGGTTCACGT AGTGGGCCAT 4140
CGCCCTGATA GACGGTTTTT CGCCCTTTGA CGTTGGAGTC CACGTTCTTT AATAGTGGAC 4200
TCTTGTTCCA AACTGGAACA ACACTCAACC CTATCTCGGG CTATTCTTTT GATTTATAAG 4260
GGATTTTGCC GATTTCGGCC TATTGGTTAA AAAATGAGCT GATTTAACAA AAATTTAACG 4320
CGAATTTTAA CAAAATATTA ACGTTTACAA TTTTATGGTG CACTCTCAGT ACAATCTGCT 4380
CTGATGCCGC ATAGTTAAGC CAACTCCGCT ATCGCTACGT GACTGGGTCA TGGCTGCGCC 4440
CCGACACCCG CCAACACCCG CTGACGCGCC CTGACGGGCT TGTCTGCTCC CGGCATCCGC 4500
TTACAGACAA GCTGTGACCG TCTCCGGGAG CTGCATGTGT CAGAGGTTTT CACCGTCATC 4560
ACCGAAACGC GCGAGGCAGT ATTCTTGAAG ACGAAAGGGC CTCGTGATAC GCCTATTTTT 4620
ATAGGTTAAT GTCATGATAA TAATGGTTTC TTAGACGTCA GGTGGCACTT TTCGGGGAAA 4680
TGTGCGCGGA ACCCCTATTT GTTTATTTTT CTAAATACAT TCAAATATGT ATCCGCTCAT 4740
GAGACAATAA CCCTGATAAA TCTTCAATA ATATTGAAAA AGGAAGAGTA TGAGTATTCAA 4800
ACATTTCCGT GTCGCCCTTA TTCCCTTTTT GGCGGCATTT TGCCTTCCTG TTTTTGCTCA 4860
CCCAGAAACG CTGGTGAAAG TAAAAGATGC TGAAGATCAG TTGGGTGCAC GAGTGGGTTA 4920
CATCGAACTG GATCTCAACA GCGGTAAGAT CCTTGAGAGT TTTCGCCCCG AAGAACGTTT 4980
TCCAATGATG AGCACTTTTA AAGTTCTGCT ATGTGGCGCG GTATTATCCC GTGATGACGC 5040
CGGGCAAGAG CAACTCGGTC GCCGCATACA CTATTCTCAG AATGACTTGG TTGAGTACTC 5100
```

FIG. 4F

```
ACCAGTCACA GAAAGCATC TTACGGATGG CATGACAGTA AGAGAATTAT GCAGTGCTGC  5160
CATAACCATG AGTGATAACA CTGCGGCCAA CTTACTTCTG ACAACGATCG GAGGACCGAA  5220
GGAGCTAACC GCTTTTTTGC ACAACATGGG GGATCATGTA ACTCGCCTTG ATCGTTGGGA  5280
ACCGGAGCTG AATGAAGCCA TACCAAACGA CGAGCGTGAC ACCACGATGC CAGCAGCAAT  5340
GGCAACAACG TTGCGCAAAC TATTAACTGG CGAACTACTT ACTCTAGCTT CCCGGCAACA  5400
ATTAATAGAC TGGATGGAGG CGGATAAAGT TGCAGGACCA CTTCTGCGCT CGGCCCTTCC  5460
GGCTGGCTGG TTTATTGCTG ATAAATCTGG AGCCGGTGAG CGTGGGTCTC GCGGTATCAT  5520
TGCAGCACTG GGGCCAGATG GTAAGCCCTC CCGTATCGTA GTTATCTACA CGACGGGGAG  5580
TCAGGCAACT ATGGATGAAC GAAATAGACA GATCGCTGAG ATAGGTGCCT CACTGATTAA  5640
GCATTGGTAA CTGTCAGACC AAGTTTACTC ATATATACTT TAGATTGATT TAAAACTTCA  5700
TTTTTAATTT AAAAGGATCT AGGTGAAGAT CCTTTTTGAT AATCTCATGA CCAAAATCCC  5760
TTAACGTGAG TTTTCGTTCC ACTGAGCGTC AGACCCCGTA GAAAAGATCA AAGGATCTTC  5820
TTGAGATCCT TTTTTTCTGC GCGTAATCTG CTGCTTGCAA ACAAAAAAAC CACCGCTACC  5880
AGCGGTGGTT TGTTTGCCGG ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT  5940
CAGCAGAGCG CAGATACCAA ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCACTT  6000
CAAGAACTCT GTAGCACCGC CTACATACCT CGCTCTGCTA ATCCTGTTAC CAGTGGCTGC  6060
TGCCAGTGGC GATAAGTCGT GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA  6120
```

FIG. 4G

```
GGCGCAGCGG TCGGGCTGAA CCGGGGGTTC GTGCACACAG CCCAGCTTGG AGCGAACGAC   6180
CTACACCGAA CTGAGATACC TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG   6240
GAGAAAGGCG GACAGGTATC CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGA   6300
GCTTCCAGGG GGAAACGCCT GGTATCTTTA TAGTCCTGTC GGGTTTCGCC ACCTCTGACT   6360
TGAGCGTCGA TTTTTGTGAT GCTCGTCAGG GGGGCGGAGC CTATGGAAAA ACGCCAGCAA   6420
CGCGGCCTTT TTACGGTTCC TGGCCTTTTG CTGGCCTTTT GCTCACATGT TCTTTCCTGC   6480
GTTATCCCCT GATTCTGTGG ATAACCGTAT TACCGCCTTT GAGTGAGCTG ATACCGCTCG   6540
CCGCAGCCGA ACGACCGAGC GCAGCGAGTC AGTGAGCGAG GAAGCGGAAG AGCGCCCAAT   6600
ACGCAAACCG CCTCTCCCCG CGCGTTGGCC GATTCATTAA TCCAGCTGGC ACGACAGGTT   6660
TCCCGACTGG AAAGCGGGCA GTGAGCGCAA CGCAATTAAT GTGAGTTACC TCACTCATTA   6720
GGCACCCCAG GCTTTACACT TTATGCTTCC GGCTCGTATG TTGTGTGGAA TTGTGAGCGG   6780
ATAACAATTT CACACAGGAA ACAGCTATGA CCATGATTAC GAATTAA                 6827
```

FIG. 4H

```
Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe Arg Ala Met Val Glu Leu
 1               5                  10                  15

Ala Arg Leu Asp Arg Arg Arg Pro Gly Ser Ser Asp Arg Val Leu Phe
            20                  25                  30

Ala Arg Phe Ser Lys Thr Glu Gly Gly Ala Arg Arg Ala Ser Pro Asp
        35                  40                  45

Gln Glu Ala Glu Asp Leu Trp Leu Ser Pro Leu Thr Met Glu Asp Leu
    50                  55                  60

Val Cys Tyr Ser Phe Gln Val Ala Arg Gly Met Glu Phe Leu Ala Ser
65                  70                  75                  80

Arg Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser
                85                  90                  95

Glu Ser Asp Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile
            100                 105                 110

Tyr Lys Asp Pro Asp Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu
        115                 120                 125

Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln
    130                 135                 140

Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu
145                 150                 155                 160

Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile Asn Glu Glu Phe Cys Gln
                165                 170                 175

Arg Leu Arg Asp Gly Thr Arg Met Arg Ala Pro Glu Leu Ala Thr Pro
            180                 185                 190
```

FIG. 4 I

```
Ala Ile Arg Arg Ile Met Leu Asn Cys Trp Ser Gly Asp Pro Lys Ala
        195                 200                 205

Arg Pro Ala Phe Ser Glu Leu Val Glu Ile Leu Gly Asp Leu Leu Gln
    210                 215                 220

Gly Arg Gly Leu Gln Glu Glu Glu Glu Val Cys Met Ala Pro Arg Ser
225                 230                 235                 240

Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser Gln Val Ser Thr Met Ala
                245                 250                 255

Leu His Ile Ala Gln Ala Asp Ala Glu Asp Ser Pro Pro Ser Leu Gln
            260                 265                 270

Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn Trp Val Ser Phe Pro Gly
        275                 280                 285

Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly Ser Ser Arg Met Lys Thr
    290                 295                 300

Phe Glu Glu Phe Pro Met Thr Pro Thr Thr Tyr Lys Gly Ser Val Asp
305                 310                 315                 320

Asn Gln Thr Asp Ser Gly Met Val Leu Ala Ser Glu Glu Cys Glu Gln
                325                 330                 335

Ile Glu Ser Arg Tyr Arg Gln Glu Ser Gly Phe Arg  *
            340                 345
```

FIG. 5A

```
TCGAGCTCG CCCGACATTG ATTATTGACT AGTTATTAAT AGTAATCAAT TACGGGGTCA      60
TTAGTTCATA GCCCATATAT GGAGTTCCGC GTTACATAAC TTACGGTAAA TGGCCCGCCT     120
GGCTGACCGC CCAACGACCC CCGCCCATTG ACGTCAATAA TGACGTATGT TCCCATAGTA     180
ACGCCAATAG GGACTTTCCA TTGACGTCAA TGGGTGGAGT ATTTACGGTA AACTGCCCAC     240
TTGGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC CTATTGACGT CAATGACGGT     300
AAATGGCCCG CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGACTTTCC TACTTGGCAG     360
TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATGC GGTTTTGGCA GTACATCAAT     420
GGGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC TCCACCCCAT TGACGTCAAT     480
GGGAGTTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC     540
CCATTGACGC AAATGGGCGG TAGGCGTGTA CGGTGGGAGG TCTATATAAG CAGAGCTCGT     600
TTAGTGAACC GTCAGATCGC CTGGAGACGC CATCCACGCT GTTTTGACCT CCATAGAAGA     660
CACCGGGACC GATCCAGCCT CCGCGGCCGG GAACGGTGCA TTGGAACGCG GATTCCCCGT     720
GCCAAGAGTG ACGTAAGTAC CGCCTATAGA GTCTATAGGC CCACTTGGCT TCGTTAGAAC     780
GCGGCTACAA TTAATACATA ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA     840
GAATAACATC CACTTTGCCT TTCTCTCCAC AGGTGTCCAC TCCCAGGTCC AACTGCACCT     900
CGGTTCTATC GATTGAATTC CCCGGGGATC CTCTAGAGAT CCCTCGACCT CGAGTCGACT     960
TTTTTTTTTT TTTTTGTAGG CCAAAGGGTA CTTCTTTTTC TTTATTAATT ACTCAGAAGT    1020
```

FIG. 5B

```
CTAGGCCACA GCAATCTACT GTTCTCCTCT CATTTTCCTA AACTATTTTG ATACCTATTT   1080
CTCAGACTTT ATGGGCTATT AGACATTTCT CACATTTCCA TAGATAATAA CTCATCCGTT   1140
TTGCAACCTG ATTCTCAATA TTAAGAGATT AAAACTAATG TATATGACTC TCAGTTGACA   1200
CATACTGAAG TACAGAAAAA TTCCATCATT TCCTTCTGCA AAATGAAAAA GACTTCGTTT   1260
TCTCAACAGC TGCATCATTT TTTTATGCAT AGAAAAAAAT GTGCAATTAC TCCAAGTACA   1320
ATCAAGTCAT TTAACATGGC TTTACCATCA TTGTAGTTAC AGGATATTTT AAAAGAGAAA   1380
AAAAAATCTC AAAGCACAGG TCCTGCTGTG CAGCAAAGCA ATCAAATTCC TTCATAATAA   1440
CAGCCTGATG GGATTCAGCA ATCTGAGGAA TAATGAATAA CCACTCTAAT CAGTAAACAG   1500
GAAAATGCTA CAACAGTCAC TGAGTAAAAA TTGGACTATC ATCTGTTGAT TCTCTTGATC   1560
GACATTTCAA ACAATAAATG GAAATGTAAG TATCTCTTAA AAAGAAAAAT AACTTGGTTT   1620
AGTGTGCTTA ATTTTACCAG GCAGTGAGGA AATTATATAT CACCTTGACT GTCCTGCAGT   1680
GTTGCCCAGT CAATAAAATG CACAAATAAT CTTTTTCATA ATACATGGCC AACTTTATCC   1740
TATCACTTGA ATATGTCAGG ATAAACTGAT TGTGCAGTTG GTTGATAACA TTGTATTTTG   1800
GAATGGATTA TTTGAATTTG TTTTGCTACT TTATTATTTG ATATTCTTCT CCAGTGTTCA   1860
TCTTATGAAG TTATTTGCAT CTGAATATGA AGAGTCTGTT TCAAAATAGT CTTCAAGTTT   1920
CCAACGCAGT GTCTCAAATG TAGGTCGTTC CTTAGGCTCT GCATTCCAGC ACTCCAACAT   1980
GATGTTGTAA AATTGCTGTG GACAGTTGGA TGGTTGCGGA AGTCTATAGT TTTGAGCCAA   2040
```

FIG. 5C

```
CATCTGGATT ACCTGGGCAC CTGTCATACC ACTGTAAGGC ATTTTGCCAT AAGTAATGAT   2100
TTCATAAAGA AGGATTCCAA ATGACCATAC ATCGGACTTA ATGCTGAATT TATTACTACG   2160
AATGGCTTCG GGCGCAGTCC ACTTCACCGG CAGCTTTATT TCGTGTCTAG ATTCATAGAT   2220
GTCTTCATTA TCTACCTTAA AAACTCTGGC AAGTCCAAAA TCTGCTACTT TGTAGATATT   2280
ATGTTCACCA ACGAGGACAT TTCTGGCAGC CAGATCTCTG TGAATGTAGT TCCGAGACTC   2340
CAGATAGGCC ATTCCAGAGG CAACCTGTGC CGCCATGTCT ACCTGTTGAG TCAGATGGAT   2400
TTTTGATCCA GTGTCATTTT GGAGATATTC TTGCAGACTT CCATGTCTCA TCAACTCTGT   2460
AATAATATAA ATTGGATCTT CTAAAGTGCA AACAGCATAA AGCTGGATAA GCTTTGGATG   2520
TCTTAGGTTC TTCATTATCT GTGCCTCCCT CAGGAAGTCA TTTGGATCCA TTGAACCTGG   2580
TTTTAATGTT TTCACTGCTA CTGGAGTGGT ATTGTTCCAC AGACCTTCCC ATACTTCGCC   2640
AAACTGACCA GATCCCAATC GCTTCAGAAG CTGTATGGAG TTGCGGTCTA TCTCCCATTG   2700
GTCCACGGTT TTATACGACA AATCAAATGG AGCTGGGACC TGGATCTTTA AGCATGGTTT   2760
CCCCAGCTTG ACACACAGGC CGTCACTTGT CTTGGTGTAG TGGCTCACAA ATTCGTTCAG   2820
TGTTGAAAAG ATTCTTCTTC GCGTGAGAAA AAATCCCCCT TCATCCAGTC TTTTAATTCT   2880
GTAGTGTTTT ACAACTGCTC CATCTAAAAC TGAAAGAGAG AATTCTCCTT TTTGGCTTTC   2940
ACTTTCTCTG ATTAGAAAGG AACCGGTCTT GTTTTCTGAA TATAATAGTT GTTTCTCTGC   3000
ATCTGATCTT CCGATTGCTC CAAAGAACCA CGGCTCTGCC TGTAGGCTTC TGTCCTCAGC   3060
```

FIG. 5D

CACGTAGTTA GAAGGAATAT AGCCTTGTAG TTGCTGACTG GAGCCATCTC GTCTTTTCTC	3120
CAAGTGTCTG GCAAACCACC AGCCCTCATG CAAAGTGTCC AGAACTTGAA GTTTGTCACC	3180
TGCTCGGAAG CTCAAGTCCT CAGCAGTCCG AGCCTGGTAA TCAAACAAAG CCACAAAGTA	3240
GTGGCCATGC CTCTGTGACT GGGGAGAGCA AAGGGCCCCT GGATTTTCAA TCACGGTTGA	3300
CTTGTCTGCC TCCGTGGACA AACAGGGGAG ATAGGGTTCT AGGTACTCCC AGAGCCTCTG	3360
ACAGATGTTG CTCATTGTGC CTTGGTGGGG AGAAGAGGAG CAGGGCTTCT CCCTCTCCCC	3420
TTAGTCTCTG CGATCCACCT TATCTTCCTT CACCAGGCAA CTTTGAAGTC AGCACCAACT	3480
CACCATACTT CGGAGAGTAT GCAAAGTCCC GTTTCAGATC AGTCCAGCAG CTGGGTTGCA	3540
GCAAGTCCTA CCTGGAGAGA CTTACCGGCT TGCTTTCTGT GGCTGGAGGT GCTACCCCGA	3600
GGCAAAACTG AGCAGGAGCT GGGCAGCTGC TCACTAGGAA GGTGTCTTTT CTTCTTATCT	3660
GCTTAAGAAT CCCACAACAA AAATAAAATA AAATTAAAAG GGCTTTATTT AGACAAATAT	3720
CTGAGAACAG AATGGTGCCA TCTTGCCTTT TGTCCCAATA AAAAGTTAGC AAGAGGAAGC	3780
TACTAACCCC TGGTAAAACC TCCACGTCTT GCTTTCGCCA GGGTCGACTC GAGGGATCTT	3840
CCATACCTAC CAGTTCTGCG CCTGCAGGTC GCGGCCGCGA CTCTAGAGTC GACCTGCAGA	3900
AGCTTGGCCG CCATGGCCCA ACTTGTTTAT TGCAGCTTAT AATGGTTACA AATAAAGCAA	3960
TAGCATCACA AATTTCACAA ATAAAGCATT TTTTTCACTG CATTCTAGTT GTGGTTTGTC	4020
CAAACTCATC AATGTATCTT ATCATGTCTG GATCGGGAAT TAATTCGGCG CAGCACCATG	4080

FIG. 5E

```
GCCTGAAATA ACCTCTGAAA GAGGAACTTG GTTAGGTACC TTCTGAGGCG GAAAGAACCA   4140
GCTGTGGAAT GTGTGTCAGT TAGGGTGTGG AAAGTCCCCA GGCTCCCCAG CAGGCAGAAG   4200
TATGCAAAGC ATGCATCTCA ATTAGTCAGC AACCAGGTGT GGAAAGTCCC CAGGCTCCCC   4260
AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA GCAACCATAG TCCCGCCCCT   4320
AACTCCGCCC ATCCCGCCCC TAACTCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG   4380
ACTAATTTTT TTTATTTATG CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC TATTCCAGAA   4440
GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA AAGCTGTTAA CAGCTTGGCA   4500
CTGGCCGTCG TTTTACAACG TCGTGACTGG GAAAACCCTG GCGTTACCCA ACTTAATCGC   4560
CTTGCAGCAC ATCCCCCTTT CGCCAGCTGG CGTAATAGCG AAGAGGCCCG CACCGATCGC   4620
CCTTCCCAAC AGTTGCGCAG CCTGAATGGC GAATGGCGCC TGATGCGGTA TTTTCTCCTT   4680
ACGCATCTGT GCGGTATTTC ACACCGCATA CGTCAAAGCA ACCATAGTAC GCGCCCTGTA   4740
GCGGCGCATT AAGCGCGGCG GGTGTGGTGG TTACGCGCAG CGTGACCGCT ACACTTGCCA   4800
GCGCCCTAGC GCCCGCTCCT TTCGCTTTCT TCCCTTCCTT TCTCGCCACG TTCGCCGGCT   4860
TTCCCCGTCA AGCTCTAAAT CGGGGGCTCC CTTTAGGGTT CCGATTTAGT GCTTTACGGC   4920
ACCTCGACCC CAAAAAACTT GATTTGGGTG ATGGTTCACG TAGTGGGCCA TCGCCCTGAT   4980
AGACGGTTTT TCGCCCTTTG ACGTTGGAGT CCACGTTCTT TAATAGTGGA CTCTTGTTCC   5040
AAACTGGAAC AACACTCAAC CCTATCTCGG GCTATTCTTT TGATTTATAA GGGATTTTGC   5100
```

FIG. 5F

```
CGATTTCGGC CTATTGGTTA AAAAATGAGC TGATTTAACA AAAATTTAAC GCGAATTTTA   5160
ACAAAATATT AACGTTTACA ATTTTATGGT GCACTCTCAG TACAATCTGC TCTGATGCCG   5220
CATAGTTAAG CCAGCCCCGA CACCCGCCAA CACCCGCTGA CGCGCCCTGA CGGGCTTGTC   5280
TGCTCCCGGC ATCCGCTTAC AGACAAGCTG TGACCGTCTC CGGGAGCTGC ATGTGTCAGA   5340
GGTTTTCACC GTCATCACCG AAACGCGCGA GACGAAAGGG CCTCGTGATA CGCCTATTTT   5400
TATAGGTTAA TGTCATGATA ATAATGGTTT CTTAGACGTC AGGTGGCACT TTTCGGGGAA   5460
ATGTGCGCGG AACCCCTATT TGTTTATTTT TCTAAATACA TTCAAATATG TATCCGCTCA   5520
TGAGACAATA ACCCTGATAA ATGCTTCAAT AATATTGAAA AAGGAAGAGT ATGAGTATTC   5580
AACATTTCCG TGTCGCCCTT ATTCCCTTTT TTGCGGCATT TTGCCTTCCT GTTTTTGCTC   5640
ACCCAGAAAC GCTGGTGAAA GTAAAAGATG CTGAAGATCA GTTGGGTGCA CGAGTGGGTT   5700
ACATCGAACT GGATCTCAAC AGCGGTAAGA TCCTTGAGAG TTTTCGCCCC GAAGAACGTT   5760
TTCCAATGAT GAGCACTTTT AAAGTTCTGC TATGTGGCGC GGTATTATCC CGTATTGACG   5820
CCGGGCAAGA GCAACTCGGT CGCCGCATAC ACTATTCTCA GAATGACTTG GTTGAGTACT   5880
CACCAGTCAC AGAAAAGCAT CTTACGGATG GCATGACAGT AAGAGAATTA TGCAGTGCTG   5940
CCATAACCAT GAGTGATAAC ACTGCGGCCA ACTTACTTCT GACAACGATC GGAGGACCGA   6000
AGGAGCTAAC CGCTTTTTTG CACAACATGG GGGATCATGT AACTCGCCTT GATCGTTGGG   6060
AACCGGAGCT GAATGAAGCC ATACCAAACG ACGAGCGTGA CACCACGATG CCTGTAGCAA   6120
```

FIG. 5G

```
TGGCAACAAC GTTGCGCAAA CTATTAACTG GCGAACTACT TACTCTAGCT TCCCGGCAAC   6180
AATTAATAGA CTGGATGGAG GCGGATAAAG TTGCAGGACC ACTTCTGCGC TCGGCCCTTC   6240
CGGCTGGCTG GTTTATTGCT GATAAATCTG GAGCCGGTGA GCGTGGGTCT CGCGGTATCA   6300
TTGCAGCACT GGGGCCAGAT GGTAAGCCCT CCCGTATCGT AGTTATCTAC ACGACGGGGA   6360
GTCAGGCAAC TATGGATGAA CGAAATAGAC AGATCGCTGA GATAGGTGCC TCACTGATTA   6420
AGCATTGGTA ACTGTCAGAC CAAGTTTACT CATATATACT TTAGATTGAT TTAAAACTTC   6480
ATTTTTAATT TAAAAGGATC TAGGTGAAGA TCCTTTTTGA TAATCTCATG ACCAAAATCC   6540
CTTAACGTGA GTTTTCGTTC CACTGAGCGT CAGACCCCGT AGAAAAGATC AAAGGATCTT   6600
CTTGAGATCC TTTTTTTCTG CGCGTAATCT GCTGCTTGCA AACAAAAAAA CCACCGCTAC   6660
CAGCGGTGGT TTGTTTGCCG GATCAAGAGC TACCAACTCT TTTTCCGAAG GTAACTGGCT   6720
TCAGCAGAGC GCAGATACCA AATACTGTTC TTCTAGTGTA GCCGTAGTTA GGCCACCACT   6780
TCAAGAACTC TGTAGCACCG CCTACATACC TCGCTCTGCT AATCCTGTTA CCAGTGGCTG   6840
CTGCCAGTGG CGATAAGTCG TGTCTTACCG GGTTGGACTC AAGACGATAG TTACCGGATA   6900
AGGCGCAGCG GTCGGGCTGA ACGGGGGGTT CGTGCACACA GCCCAGCTTG GAGCGAACGA   6960
CCTACACCGA ACTGAGATAC CTACAGCGTG AGCTATGAGA AAGCGCCACG CTTCCCGAAG   7020
GGAGAAAGGC GGACAGGTAT CCGGTAAGCG GCAGGGTCGG AACAGGAGAG CGCACGAGGG   7080
AGCTTCCAGG GGGAAACGCC TGGTATCTTT ATAGTCCTGT CGGGTTTCGC CACCTCTGAC   7140
```

FIG. 5H

```
TTGAGCGTCG ATTTTTGTGA TGCTCGTCAG GGGGGCGGAG CCTATGGAAA AACGCCAGCA   7200
ACGCGGCCTT TTTACGGTTC CTGGCCTTTT GCTGGCCTTT TGCTCACATG TTCTTTCCTG   7260
CGTTATCCCC TGATTCTGTG GATAACCGTA TTACCGCCTT TGAGTGAGCT GATACCGCTC   7320
GCCGCAGCCG AACGACCGAG CGCAGCGAGT CAGTGAGCGA GGAAGCGGAA GAGCGCCCAA   7380
TACGCAAACC GCCTCTCCCC GCGCGTTGGC CGATTCATTA ATGCAGCTGG CACGACAGGT   7440
TTCCCGACTG GAAAGCGGGC AGTGAGCGCA ACGCAATTAA TGTGAGTTAG CTCACTCATT   7500
AGGCACCCCA GGCTTTACAC TTTATGCTTC CGGCTCGTAT GTTGTGTGGA ATTGTGAGCG   7560
GATAACAATT TCACACAGGA AACAGCTATG ACATGATTAC GAATTAA                 7607
```

FIG. 5I

```
Met Ser Asn Ile Cys Gln Arg Leu Trp Glu Tyr Leu Glu Pro Tyr Leu
 1               5                  10                  15

Pro Cys Leu Ser Thr Glu Ala Asp Lys Ser Thr Val Ile Glu Asn Pro
            20                  25                  30

Gly Ala Leu Cys Ser Pro Gln Ser Gln Arg His Gly His Tyr Phe Val
        35                  40                  45

Ala Leu Phe Asp Tyr Gln Ala Arg Thr Ala Glu Asp Leu Ser Phe Arg
    50                  55                  60

Ala Gly Asp Lys Leu Gln Val Leu Asp Thr Leu His Glu Gly Trp Trp
65                  70                  75                  80

Phe Ala Arg His Leu Glu Lys Arg Arg Asp Gly Ser Ser Gln Gln Leu
                85                  90                  95

Gln Gly Tyr Ile Pro Ser Asn Tyr Val Ala Glu Asp Arg Ser Leu Gln
            100                 105                 110

Ala Glu Pro Trp Phe Phe Gly Ala Ile Gly Arg Ser Asp Ala Glu Lys
        115                 120                 125

Gln Leu Leu Tyr Ser Glu Asn Lys Thr Gly Ser Phe Leu Ile Arg Glu
    130                 135                 140

Ser Glu Ser Gln Lys Gly Glu Phe Ser Leu Ser Val Leu Asp Gly Ala
145                 150                 155                 160

Val Val Lys His Tyr Arg Ile Lys Arg Leu Asp Glu Gly Gly Phe Phe
                165                 170                 175

Leu Thr Arg Arg Arg Ile Phe Ser Thr Leu Asn Glu Phe Val Ser His
            180                 185                 190
```

FIG. 5J

```
Tyr Thr Lys Thr Ser Asp Gly Leu Cys Val Lys Leu Gly Lys Pro Cys
        195                 200                 205

Leu Lys Ile Gln Val Pro Ala Pro Phe Asp Leu Ser Tyr Lys Thr Val
    210                 215                 220

Asp Gln Trp Glu Ile Asp Arg Asn Ser Ile Gln Leu Leu Lys Arg Leu
225                 230                 235                 240

Gly Ser Gly Gln Phe Gly Glu Val Trp Glu Gly Leu Trp Asn Asn Thr
                245                 250                 255

Thr Pro Val Ala Val Lys Thr Leu Lys Pro Gly Ser Met Asp Pro Asn
            260                 265                 270

Asp Phe Leu Arg Glu Ala Gln Ile Met Lys Asn Leu Arg His Pro Lys
        275                 280                 285

Leu Ile Gln Leu Tyr Ala Val Cys Thr Leu Glu Asp Pro Ile Tyr Ile
    290                 295                 300

Ile Thr Glu Leu Met Arg His Gly Ser Leu Gln Glu Tyr Leu Gln Asn
305                 310                 315                 320

Asp Thr Gly Ser Lys Ile His Leu Thr Gln Gln Val Asp Met Ala Ala
                325                 330                 335

Gln Val Ala Ser Gly Met Ala Tyr Leu Glu Ser Arg Asn Tyr Ile His
            340                 345                 350

Arg Asp Leu Ala Ala Arg Asn Val Leu Val Gly Glu His Asn Ile Tyr
        355                 360                 365

Lys Val Ala Asp Phe Gly Leu Ala Arg Val Phe Lys Val Asp Asn Glu
    370                 375                 380
```

FIG. 5K

```
Asp Ile Tyr Glu Ser Arg His Glu Ile Lys Leu Pro Val Lys Trp Thr
385                 390                 395                 400

Ala Pro Glu Ala Ile Arg Ser Asn Lys Phe Ser Ile Lys Ser Asp Val
                405                 410                 415

Trp Ser Phe Gly Ile Leu Leu Tyr Glu Ile Ile Thr Tyr Gly Lys Met
            420                 425                 430

Pro Tyr Ser Gly Met Thr Gly Ala Gln Val Ile Gln Met Leu Ala Gln
        435                 440                 445

Asn Tyr Arg Leu Pro Gln Pro Ser Asn Cys Pro Gln Gln Phe Tyr Asn
    450                 455                 460

Ile Met Leu Glu Cys Trp Asn Ala Glu Pro Lys Glu Arg Pro Thr Phe
465                 470                 475                 480

Glu Thr Leu Arg Trp Lys Leu Glu Asp Tyr Phe Glu Thr Asp Ser Ser
                485                 490                 495

Tyr Ser Asp Ala Asn Asn Phe Ile Arg *
            500                 505
```

FIG. 6

```
GCGGCCGCAG AGAAAGCAGA GGATGGGGCT TAGCAGCTGG CAGAGCCAGG AGCGGGGAGG      60
TAGCAGAAAG ACCACAAGTA CAAAGAAGTC CTGAAACTTT GGTTTTGCTG CTGCAGCCCA     120
TTGAGAGTGA CGACATGGAG CACAAGACCC TGAAGATCAC CGACTTTGGC CTGGCCCGAG     180
AGTGGCACAA AACCACACAA ATGAGTGCCG CNGGCACCTA CNCCTGGATG GCTCCTGAGG     240
TTATCAAGGC CTCCACCTTC TCTAAGGGCA GTGACGTCTG GAGTTTTGGG GTGCTGCTGT     300
GGGAACTGCT GACCGGGGAG NTGCCATACC GTGGCATTGA CTGCCTTGCT GTGGCCTATG     360
GCGTAGCTGT TAACAAGCTC ACACTGCCAT CCATCCACCT GGCC                       404
```

FIG. 7A

```
ATGAGAGCGT TGGCGCGCGA CGGCGGCCAG CTGCCGCTGC TCGTTGTTTT TTCTGCAATG      60
ATATTTGGGA CTATTACAAA TCAAGATCTG CCTGTGATCA AGTGTGTTTT AATCAATCAT     120
AAGAACAATG ATTCATCAGT GGGGAAGTCA TCATCATATC CCATGGTATC AGAATCCCCG     180
GAAGACCTCG GGTGTGCGTT GAGACCCCAG AGCTCAGGGA CAGTGTACGA AGCTGCCGCT     240
GTGGAAGTGG ATGTATCTGC TTCCATCACA CTGCAAGTGC TGGTCGATGC CCCAGGGAAC     300
ATTTCCTGTC TCTGGGTCTT TAAGCACAGC TCCCTGAATT GCCAGCCACA TTTTGATTTA     360
CAAAACAGAG GAGTTGTTTC CATCGTCATT TTGAAAATGA CAGAAACCCA AGCTGGAGAA     420
TACCTACTTT TTATTCAGAG TGAAGCTACC AATTACACAA TATTGTTTAC AGTGAGTATA     480
AGAAATACCC TGCTTTACAC ATTAAGAAGA CCTTACTTTA GAAAATGGA AAACCAGGAC     540
GCCCTGGTCT GCATATCTGA GAGCGTTCCA GAGCGGATCC TGGAATGGGT GCTTTGCGAT     600
TCACAGGGGG AAAGCTGTAA AGAAGAAAGT CCAGCTGTTG TTAAAAAGGA GGAAAAAGTG     660
CTTCATGAAT TATTTGGGAC GGACATAAGG TGCTGTGCCA GAAATGAACT GGGCAGGGAA     720
TGCACCAGGC TGTTCACAAT AGATCTAAAT CAAACTCCTC AGACCACATT GCCACAATTA     780
TTTCTTAAAG TAGGGGAACC CTTATGGATA AGGTGCAAAG CTGTTCATGT GAACCATGGA     840
TTCGGGCTCA CCTGGGAATT AGAAAACAAA GCACTCGAGG AGGGCAACTA CTTTGAGATG     900
AGTACCTATT CAACAACAG AACTATGATA CGGATTCTGT TTGCTTTTGT ATCATCAGTG     960
GCAAGAAACG ACACCGGATA CTACACTTGT TCCTCTTCAA AGCATCCCAG TCAATCAGCT    1020
TTGGTTACCA TCGTAGAAAA GGGATTTATA AATGCTACCA ATTCAAGTGA AGATTATGAA    1080
```

FIG. 7B

```
ATTGACCAAT ATGAAGAGTT TTGTTTTTCT GTCAGGTTTA AAGCCTACCC ACAAATCAGA 1140
TGTACGTGGA CCTTCTCTCG AAAATCATTT CCTTGTGAGC AAAAGGGTCT TGATAACGGA 1200
TACAGCATAT CCAAGTTTTG CAATCATAAG CACCAGCCAG GAGAATATAT ATTCCATGCA 1260
GAAAATGATG ATGCCCAATT TACCAAAATG TTCACGCTGT ATATAAGAAG GAAACCTCAA 1320
GTCCTCGCAG AAGCTTCGGC AAGTCAGGCG TCCTGTTTCT CGGATGGATA CCCATTACCA 1380
TCTTGGACCT GGAAGAAGTG TTCAGACAAG TCTCCCAACT GCACAGAAGA GATCACAGAA 1440
GGAGTCTGGA ATAGAAAGGC TAACAGAAAA GTGTTTGGAC AGTGGGTGTC GAGCAGTACT 1500
CTAAACATGA GTGAAGCCAT AAAAGGGTTC CTGGTCAAGT GCTGTGCATA CAATTCCCTT 1560
GGCACATCTT GTGAGACGAT CCTTTTAAAC TCTCCAGGCC CCTTCCCTTT CATCCAAGAC 1620
AACATCTCAT TCTATGCAAC AATTGGTGTT TGTCTCCTCT TCATTGTCGT TTTAACCCTG 1680
CTAATTTGTC ACAAGTACAA AAAGCAATTT AGGTATGAAA GCCAGCTACA GATGGTACAG 1740
GTGACCGGAT CCTCAGATTA TGAGTACTTC TACGTTGATT TCAGAGAATA TGAATATGAT 1800
GTCAAATGGG AGTTTCCAAG AGAAAATTTA GAGTTTGGGA AGGTACTAGG ATCAGGTGCT 1860
TTTGGAAAAG TGATGAACGC AACAGCTTAT GGAATTAGCA AAACAGGAGT CTCAATCCAG 1920
GTTACCGTCA AAATGCTGAA AGAAAAAGCA GACAGCTCTG AAAGAGAGGC ACTCATGTCA 1980
GAACTCAAGA TGATGACCCA GCTGGGAAGC CACGAGAATA TTGTGAACCT GCTGGGGGCG 2040
TGCACACTGT CAGGACCAAT TTACTTGATT TTTGAATACT GTTGCTATGG TGATCTTCTC 2100
AACTATCTAA GAAGTAAAAG AGAAAAATTT CACAGGACTT GGACAGAGAT TTTCAAGGAA 2160
```

FIG. 7C

CACAATTTCA GTTTTTACCC CACTTTCCAA TCACATCCAA ATTCCAGCAT GCCTGGTTCA	2220
AGAGAAGTTC AGATACACCC GGACTCGGAT CAAATCTCAG GGCTTCATGG GAATTCATTT	2280
CACTCTGAAG ATGAAATTGA ATATGAAAAC CAAAAAGGC TGGAAGAAGA GGAGGACTTG	2340
AATGTGCTTA CATTTGAAGA TCTTCTTTGC TTTGCATATC AAGTTGCCAA AGGAATGGAA	2400
TTTCTGGAAT TTAAGTCGTG TGTTCACAGA GACCTGGCCG CCAGGAACGT GCTTGTCACC	2460
CACGGGAAAG TGGTGAAGAT ATGTGACTTT GGATTGGCTC GAGATATCAT GAGTGATTCC	2520
AACTATGTTG TCAGGGGCAA TGCCCGTCTG CCTGTAAAAT GGATGGCCCC CGAAAGCCTG	2580
TTTGAAGGCA TCTACACCAT TAAGAGTGAT GTCTGGTCAT ATGGAATATT ACTGTGGGAA	2640
ATCTTCTCAC TTGGTGTGAA TCCTTACCCT GGCATTCCGG TTGATGCTAA CTTCTACAAA	2700
CTGATTCAAA ATGGATTTAA AATGGATCAG CCATTTTATG CTACAGAAGA AATATACATT	2760
ATAATGCAAT CCTGCTGGGC TTTTGACTCA AGGAAACGGC CATCCTTCCC TAATTTGACT	2820
TCGTTTTTAG GATGTCAGCT GGCAGATGCA GAAGAAGCGA TGTATCAGAA TGTGGATGGC	2880
CGTGTTTCGG AATGTCCTCA CACCTACCAA AACAGGCGAC CTTTCAGCAG AGAGATGGAT	2940
TTGGGGCTAC TCTCTCCGCA GGCTCAGGTC GAAGATTCGT AGAGGAACAA TTTAGTTTTA	3000
AGGACTTCAT CCCTCCACCT ATCCCTAACA GGCTGTAGAT TACCAAAACA AGGTTAATTT	3060
CATCACTAAA AGAAAAATCTA TTATCAACTG CTGCTTCACC AGACTTTTCT CTAGAGAGCG	3120

FIG. 8A

```
TCGGCGTCCA CCCGCCCAGG GAGAGTCAGA CCTGGGGGGG CGAGGGCCCC CCAAACTCAG      60

TTCGGATCCT ACCCGAGTGA GGCGGCGCC ATG GAG CTC CGG GTG CTG CTC TGC       113
                                Met Glu Leu Arg Val Leu Leu Cys
                                  1               5

TGG GCT TCG TTG GCC GCA GCT TTG GAA GAG ACC CTG CTG AAC ACA AAA       161
Trp Ala Ser Leu Ala Ala Ala Leu Glu Glu Thr Leu Leu Asn Thr Lys
     10                  15                  20

TTG GAA ACT GCT GAT CTG AAG TGG GTG ACA TTC CCT CAG GTG GAC GGG       209
Leu Glu Thr Ala Asp Leu Lys Trp Val Thr Phe Pro Gln Val Asp Gly
 25                  30                  35                  40

CAG TGG GAG GAA CTG AGC GGC CTG GAT GAG GAA CAG CAC AGC GTG CGC       257
Gln Trp Glu Glu Leu Ser Gly Leu Asp Glu Glu Gln His Ser Val Arg
                45                  50                  55

ACC TAC GAA GTG TGT GAC GTG CAG CGT GCC CCG GGC CAG GCC CAC TGG       305
Thr Tyr Glu Val Cys Asp Val Gln Arg Ala Pro Gly Gln Ala His Trp
            60                  65                  70

CTT CGC ACA GGT TGG GTC CCA CGG CGG GGC GCC GTC CAC GTG TAC GCC       353
Leu Arg Thr Gly Trp Val Pro Arg Arg Gly Ala Val His Val Tyr Ala
        75                  80                  85

ACG CTG CGC TTC ACC ATG CTC GAG TGC CTG TCC CTG CCT CGG GCT GGG       401
Thr Leu Arg Phe Thr Met Leu Glu Cys Leu Ser Leu Pro Arg Ala Gly
     90                  95                  100

CGC TCC TGC AAG GAG ACC TTC ACC GTC TTC TAC TAT GAG AGC GAT GCG       449
Arg Ser Cys Lys Glu Thr Phe Thr Val Phe Tyr Tyr Glu Ser Asp Ala
105                 110                 115                 120

GAC ACG GCC ACG GCC CTC ACG CCA GCC TGG ATG GAG AAC CCC TAC ATC       497
Asp Thr Ala Thr Ala Leu Thr Pro Ala Trp Met Glu Asn Pro Tyr Ile
                125                 130                 135
```

FIG. 8B

```
AAG GTG GAC ACG GTG GCC GCG GAG CAT CTC ACC CGG AAG CGC CCT GGG          545
Lys Val Asp Thr Val Ala Ala Glu His Leu Thr Arg Lys Arg Pro Gly
            140                 145                 150

GCC GAG GCC ACC GGG AAG GTG AAT GTC AAG ACG CTG CGT CTG GGA CCG          593
Ala Glu Ala Thr Gly Lys Val Asn Val Lys Thr Leu Arg Leu Gly Pro
        155                 160                 165

CTC AGC AAG GCT GGC TTC TAC CTG GCC TTC CAG GAC CAG GGT GCC TGC          641
Leu Ser Lys Ala Gly Phe Tyr Leu Ala Phe Gln Asp Gln Gly Ala Cys
    170                 175                 180

ATG GCC CTG CTA TCC CTG CAC CTC TTC TAC AAA AAG TGC GCC CAG CTG          689
Met Ala Leu Leu Ser Leu His Leu Phe Tyr Lys Lys Cys Ala Gln Leu
185                 190                 195                 200

ACT GTG AAC CTG ACT CGA TTC CCG GAG ACT GTG CCT CGG GAG CTG GTT          737
Thr Val Asn Leu Thr Arg Phe Pro Glu Thr Val Pro Arg Glu Leu Val
                205                 210                 215

GTG CCC GTG GCC GGT AGC TGC GTG GTG GAT GCC GTC CCC GCC CCT GGC          785
Val Pro Val Ala Gly Ser Cys Val Val Asp Ala Val Pro Ala Pro Gly
            220                 225                 230

CCC AGC CCC AGC CTC TAC TGC CGT GAG GAT GGC CAG TGG GCC GAA CAG          833
Pro Ser Pro Ser Leu Tyr Cys Arg Glu Asp Gly Gln Trp Ala Glu Gln
        235                 240                 245

CCG GTC ACG GGC TGC AGC TGT GCT CCG GGG TTC GAG GCA GCT GAG GGG          881
Pro Val Thr Gly Cys Ser Cys Ala Pro Gly Phe Glu Ala Ala Glu Gly
    250                 255                 260

AAC ACC AAG TGC CGA GCC TGT GCC CAG GGC ACC TTC AAG CCC CTG TCA          929
Asn Thr Lys Cys Arg Ala Cys Ala Gln Gly Thr Phe Lys Pro Leu Ser
265                 270                 275                 280
```

FIG. 8C

```
GGA GAA GGG TCC TGC CAG CCA TGC CCA GCC AAT AGC CAC TCT AAC ACC          977
Gly Glu Gly Ser Cys Gln Pro Cys Pro Ala Asn Ser His Ser Asn Thr
                285                 290                 295

ATT GGA TCA GCC GTC TGC CAG TGC CGC GTC GGG TAC TTC CGG GCA CGC         1025
Ile Gly Ser Ala Val Cys Gln Cys Arg Val Gly Tyr Phe Arg Ala Arg
            300                 305                 310

ACA GAC CCC CGG GGT GCA CCC TGC ACC ACC CCT CCT TCG GCT CCG CGG         1073
Thr Asp Pro Arg Gly Ala Pro Cys Thr Thr Pro Pro Ser Ala Pro Arg
        315                 320                 325

AGC GTG GTT TCC CGC CTG AAC GGC TCC TCC CTG CAC CTG GAA TGG AGT         1121
Ser Val Val Ser Arg Leu Asn Gly Ser Ser Leu His Leu Glu Trp Ser
    330                 335                 340

GCC CCC CTG GAG TCT GGT GGC CGA GAG GAC CTC ACC TAC GCC CTC CGC         1169
Ala Pro Leu Glu Ser Gly Gly Arg Glu Asp Leu Thr Tyr Ala Leu Arg
345                 350                 355                 360

TGC CGG GAG TGC CGA CCC GGA GGC TCC TGT GCG CCC TGC GGG GGA GAC         1217
Cys Arg Glu Cys Arg Pro Gly Gly Ser Cys Ala Pro Cys Gly Gly Asp
                365                 370                 375

CTG ACT TTT GAC CCC GGC CCC CGG GAC CTG GTG GAG CCC TGG GTG GTG         1265
Leu Thr Phe Asp Pro Gly Pro Arg Asp Leu Val Glu Pro Trp Val Val
            380                 385                 390

GTT CGA GGG CTA CGT CCT GAC TTC ACC TAT ACC TTT GAG GTC ACT GCA         1313
Val Arg Gly Leu Arg Pro Asp Phe Thr Tyr Thr Phe Glu Val Thr Ala
        395                 400                 405

TTG AAC GGG GTA TCC TCC TTA GCC ACG GGG CCC GTC CCA TTT GAG CCT         1361
Leu Asn Gly Val Ser Ser Leu Ala Thr Gly Pro Val Pro Phe Glu Pro
    410                 415                 420
```

FIG. 8D

```
GTC AAT GTC ACC ACT GAC CGA GAG GTA CCT CCT GCA GTG TCT GAC ATC          1409
Val Asn Val Thr Thr Asp Arg Glu Val Pro Pro Ala Val Ser Asp Ile
425                 430                 435                 440

CGG GTG ACG CGG TCC TCA CCC AGC AGC TTG AGC CTG GCC TGG GCT GTT          1457
Arg Val Thr Arg Ser Ser Pro Ser Ser Leu Ser Leu Ala Trp Ala Val
                445                 450                 455

CCC CGG GCA CCC AGT GGG GCT GTG CTG GAC TAC GAG GTC AAA TAC CAT          1505
Pro Arg Ala Pro Ser Gly Ala Val Leu Asp Tyr Glu Val Lys Tyr His
            460                 465                 470

GAG AAG GGC GCC GAG GGT CCC AGC AGC GTG CGG TTC CTG AAG ACG TCA          1553
Glu Lys Gly Ala Glu Gly Pro Ser Ser Val Arg Phe Leu Lys Thr Ser
        475                 480                 485

GAA AAC CGG GCA GAG CTG CGG GGG CTG AAG CGG GGA GCC AGC TAC CTG          1601
Glu Asn Arg Ala Glu Leu Arg Gly Leu Lys Arg Gly Ala Ser Tyr Leu
    490                 495                 500

GTG CAG GTA CGG GCG CGC TCT GAG GCC GGC TAC GGG CCC TTC GGC CAG          1649
Val Gln Val Arg Ala Arg Ser Glu Ala Gly Tyr Gly Pro Phe Gly Gln
505                 510                 515                 520

GAA CAT CAC AGC CAG ACC CAA CTG GAT GAG AGC GAG GGC TGG CGG GAG          1697
Glu His His Ser Gln Thr Gln Leu Asp Glu Ser Glu Gly Trp Arg Glu
                525                 530                 535

CAG CTG GCC CTG ATT GCG GGC ACG GCA GTC GTG GGT GTG GTC CTG GTC          1745
Gln Leu Ala Leu Ile Ala Gly Thr Ala Val Val Gly Val Val Leu Val
            540                 545                 550

CTG GTG GTC ATT GTG GTC GCA GTT CTC TGC CTC AGG AAG CAG AGC AAT          1793
Leu Val Val Ile Val Val Ala Val Leu Cys Leu Arg Lys Gln Ser Asn
        555                 560                 565
```

FIG. 8E

```
GGG AGA GAA GCA GAA TAT TCG GAC AAA CAC GGA CAG TAT CTC ATC GGA      1841
Gly Arg Glu Ala Glu Tyr Ser Asp Lys His Gly Gln Tyr Leu Ile Gly
    570                 575                 580

CAT GGT ACT AAG GTC TAC ATC GAC CCC TTC ACT TAT GAA GAC CCT AAT      1889
His Gly Thr Lys Val Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn
585                 590                 595                 600

GAG GCT GTG AGG GAA TTT GCA AAA GAG ATC GAT GTC TCC TAC GTC AAG      1937
Glu Ala Val Arg Glu Phe Ala Lys Glu Ile Asp Val Ser Tyr Val Lys
                605                 610                 615

ATT GAA GAG GTG ATT GGT GCA GGT GAG TTT GGC GAG GTG TGC CGG GGG      1985
Ile Glu Glu Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Arg Gly
            620                 625                 630

CGG CTC AAG GCC CCA GGG AAG AAG GAG AGC TGT GTG GCA ATC AAG ACC      2033
Arg Leu Lys Ala Pro Gly Lys Lys Glu Ser Cys Val Ala Ile Lys Thr
        635                 640                 645

CTG AAG GGT GGC TAC ACG GAG CGG CAG CGG CGT GAG TTT CTG AGC GAG      2081
Leu Lys Gly Gly Tyr Thr Glu Arg Gln Arg Arg Glu Phe Leu Ser Glu
    650                 655                 660

GCC TCC ATC ATG GGC CAG TTC GAG CAC CCC AAT ATC ATC CGC CTG GAG      2129
Ala Ser Ile Met Gly Gln Phe Glu His Pro Asn Ile Ile Arg Leu Glu
665                 670                 675                 680

GGC GTG GTC ACC AAC AGC ATG CCC GTC ATG ATT CTC ACA GAG TTC ATG      2177
Gly Val Val Thr Asn Ser Met Pro Val Met Ile Leu Thr Glu Phe Met
                685                 690                 695

GAG AAC GGC GCC CTG GAC TCC TTC CTG CGG CTA AAC GAC GGA CAG TTC      2225
Glu Asn Gly Ala Leu Asp Ser Phe Leu Arg Leu Asn Asp Gly Gln Phe
            700                 705                 710
```

FIG. 8F

```
ACA GTC ATC CAG CTC GTG GGC ATG CTG CGG GGC ATC GCC TCG GGC ATG      2273
Thr Val Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met
        715                 720                 725

CGG TAC CTT GCC GAG ATG AGC TAC GTC CAC CGA GAC CTG GCT GCT CGC      2321
Arg Tyr Leu Ala Glu Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg
    730                 735                 740

AAC ATC CTA GTC AAC AGC AAC CTC GTC TGC AAA GTG TCT GAC TTT GGC      2369
Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly
745                 750                 755                 760

CTT TCC CGA TTC CTG GAG GAG AAC TCT TCC GAT CCC ACC TAC ACG AGC      2417
Leu Ser Arg Phe Leu Glu Glu Asn Ser Ser Asp Pro Thr Tyr Thr Ser
                765                 770                 775

TCC CTG GGA GGA AAG ATT CCC ATC CGA TGG ACT GCC CCG GAG GCC ATT      2465
Ser Leu Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile
            780                 785                 790

GCC TTC CGG AAG TTC ACT TCC GCC AGT GAT GCC TGG AGT TAC GGG ATT      2513
Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Ala Trp Ser Tyr Gly Ile
        795                 800                 805

GTG ATG TGG GAG GTG ATG TCA TTT GGG GAG AGG CCG TAC TGG GAC ATG      2561
Val Met Trp Glu Val Met Ser Phe Gly Glu Arg Pro Tyr Trp Asp Met
    810                 815                 820

AGC AAT CAG GAC GTG ATC AAT GCC ATT GAA CAG GAC TAC CGG CTG CCC      2609
Ser Asn Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro
825                 830                 835                 840

CCG CCC CCA GAC TGT CCC ACC TCC CTC CAC CAG CTC ATG CTG GAC TGT      2657
Pro Pro Pro Asp Cys Pro Thr Ser Leu His Gln Leu Met Leu Asp Cys
                845                 850                 855
```

FIG. 8G

```
TGG CAG AAA GAC CGG AAT GCC CGG CCC CGC TTC CCC CAG GTG GTC AGC      2705
Trp Gln Lys Asp Arg Asn Ala Arg Pro Arg Phe Pro Gln Val Val Ser
                860                 865                 870

GCC CTG GAC AAG ATG ATC CGG AAC CCC GCC AGC CTC AAA ATC GTG GCC      2753
Ala Leu Asp Lys Met Ile Arg Asn Pro Ala Ser Leu Lys Ile Val Ala
            875                 880                 885

CGG GAG AAT GGC GGG GCC TCA CAC CCT CTC CTG GAC CAG CGG CAG CCT      2801
Arg Glu Asn Gly Gly Ala Ser His Pro Leu Leu Asp Gln Arg Gln Pro
        890                 895                 900

CAC TAC TCA GCT TTT GGC TCT GTG GGC GAG TGG CTT CGG GCC ATC AAA      2849
His Tyr Ser Ala Phe Gly Ser Val Gly Glu Trp Leu Arg Ala Ile Lys
    905                 910                 915                 920

ATG GGA AGA TAC GAA AGT TTC GCA GCC GCT GGC TTT GGC TCC TTC      2897
Met Gly Arg Tyr Glu Ser Phe Ala Ala Ala Gly Phe Gly Ser Phe
                925                 930                 935

GAG CTG GTC AGC CAG ATC TCT GCT GAG GAC CTG CTC CGA ATC GGA GTC      2945
Glu Leu Val Ser Gln Ile Ser Ala Glu Asp Leu Leu Arg Ile Gly Val
            940                 945                 950

ACT CTG GCG GGA CAC CAG AAG AAA ATC TTG GCC AGT GTC CAG CAC ATG      2993
Thr Leu Ala Gly His Gln Lys Lys Ile Leu Ala Ser Val Gln His Met
        955                 960                 965

AAG TCC CAG GCC AAG CCG GGA ACC CCG GGT GGG ACA GGA GGA CCG GCC      3041
Lys Ser Gln Ala Lys Pro Gly Thr Pro Gly Gly Thr Gly Gly Pro Ala
    970                 975                 980

CCG CAG TAC TGA CCT GCA GGA ACT CCC CAC CCC AGG GAC ACC GCC TCC      3089
Pro Gln Tyr *  Pro Ala Gly Thr Pro His Pro Arg Asp Thr Ala Ser
985                 990                 995                 1000
```

FIG. 8H

```
CCA TTT TCC GGG GCA GAG TGG GGA CTC ACA GAG GCC CCC AGC CCT GTG          3137
Pro Phe Ser Gly Ala Glu Trp Gly Leu Thr Glu Ala Pro Ser Pro Val
                1005                1010                1015

CCC CGC TGG ATT GCA CTT TGA GCC CGT GGG GTG AGG AGT TGG CAA TTT          3185
Pro Arg Trp Ile Ala Leu  *  Ala Arg Gly Val Arg Ser Trp Gln Phe
            1020                1025                1030

GGA GAG ACA GGA TTT GGG GGT TCT GCC ATA ATA GGA GGG GAA AAT CAC          3233
Gly Glu Thr Gly Phe Gly Gly Ser Ala Ile Ile Gly Gly Glu Asn His
        1035                1040                1045

CCC CCA GCC ACC TCG GGG AAC TCC AGA CCA AGG GTG AGG GCG CCT TTC          3281
Pro Pro Ala Thr Ser Gly Asn Ser Arg Pro Arg Val Arg Ala Pro Phe
    1050                1055                1060

CCT CAG GAC TGG GTG TGA CCA GAG GAA AAG GAA GTG CCC AAC ATC TCC          3329
Pro Gln Asp Trp Val  *  Pro Glu Glu Lys Glu Val Pro Asn Ile Ser
1065                1070                1075                1080

CAG CCT CCC CAG GTG CCC CCC TCA CCT TGA TGG GTG CGT TCC CGC AGA          3377
Gln Pro Pro Gln Val Pro Pro Ser Pro  *  Trp Val Arg Ser Arg Arg
                1085                1090                1095

CCA AAG AGA GTG TGA CTC CCT TGC CAG CTC CAG AGT GGG GGG GCT GTC          3425
Pro Lys Arg Val  *  Leu Pro Cys Gln Leu Gln Ser Gly Gly Ala Val
            1100                1105                1110

CCA GGG GGC AAG AAG GGG TGT CAG GGC CCA GTG ACA AAA TCA TTG GGG          3473
Pro Gly Gly Lys Lys Gly Cys Gln Gly Pro Val Thr Lys Ser Leu Gly
        1115                1120                1125

TTT GTA GTC CCA ACT TGC TGC TGT CAC CAC CAA ACT CAA TCA TTT TTT          3521
Phe Val Val Pro Thr Cys Cys Cys His His Gln Thr Gln Ser Phe Phe
    1130                1135                1140
```

FIG. 8I

```
TCC CTT GTA AAT GCC CCT CCC CCA GCT GCT GCC TTC ATA TTG AAG GTT          3569
Ser Leu Val Asn Ala Pro Pro Pro Ala Ala Ala Phe Ile Leu Lys Val
1145                1150                1155                1160

TTT GAG TTT TGT TTT TGG TCT TAA TTT TTC TCC CCG TTC CCT TTT TGT          3617
Phe Glu Phe Cys Phe Trp Ser  *  Phe Phe Ser Pro Phe Pro Phe Cys
                    1165                1170                1175

TTC TTC GTT TTG TTT TTC TAC CGT CCT TGT CAT AAC TTT GTG TTG GAG          3665
Phe Phe Val Leu Phe Phe Tyr Arg Pro Cys His Asn Phe Val Leu Glu
            1180                1185                1190

GGA ACC TGT TTC ACT ATG GCC TCC TTT GCC CAA GTT GAA ACA GGG GCC          3713
Gly Thr Cys Phe Thr Met Ala Ser Phe Ala Gln Val Glu Thr Gly Ala
        1195                1200                1205

CAT CAT CAT GTC TGT TTC CAG AAC AGT GCC TTG GTC ATC CCA CAT CCC          3761
His His His Val Cys Phe Gln Asn Ser Ala Leu Val Ile Pro His Pro
    1210                1215                1220

CGG ACC CCG CCT GGG ACC CCC AAG CTG TGT CCT ATG AAG GGG TGT GGG          3809
Arg Thr Pro Pro Gly Thr Pro Lys Leu Cys Pro Met Lys Gly Cys Gly
1225                1230                1235                1240

GTG AGG TAG TGA AAA GGG CGG TAG TTG GTG GTG GAA CCC AGA AAC GGA          3857
Val Arg  *   *  Lys Gly Arg  *  Leu Val Val Glu Pro Arg Asn Gly
                    1245                1250                1255

CGC CGG TGC TTG GAG GGG TTC TTA AAT TAT ATT TAA AAA AGT AAC TTT          3905
Arg Arg Cys Leu Glu Gly Phe Leu Asn Tyr Ile  *  Lys Ser Asn Phe
            1260                1265                1270

TTG TAT AAA TAA AAG AAA ATG GGA CGT GTC CCA GCT CCA GGG GTA              3950
Leu Tyr Lys  *  Lys Lys Met Gly Arg Val Pro Ala Pro Gly Val
        1275                1280                1285

AAAAAAAAAA AAAAAAAAA                                                    3969
```

FIG. 9

```
Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp
1               5                  10                  15

Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr
            20                  25                  30

Thr Ser Ala Leu Gly Gly Lys Ile Pro Met Arg Trp Thr Ala Pro Glu
        35                  40                  45

Ala Ile Gln Tyr Arg Lys Phe Ala Ser Ala Ser
    50                  55
```

FIG. 10

```
Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe Gly
1               5                  10                  15

Leu Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala Asp Gly
            20                  25                  30

Gly Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile His Tyr Arg
        35                  40                  45

Lys Phe Thr His Gln Ser
    50
```

FIG. 11

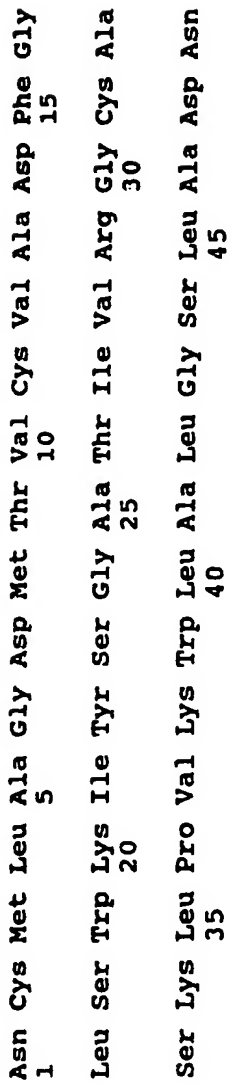
Asn Cys Met Leu Ala Gly Asp Met Thr Val Cys Val Ala Asp Phe Gly
1 5 10 15
Leu Ser Trp Lys Ile Tyr Ser Gly Ala Thr Ile Val Arg Gly Cys Ala
20 25 30
Ser Lys Leu Pro Val Lys Trp Leu Ala Leu Gly Ser Leu Ala Asp Asn
35 40 45
Leu Tyr Thr Val His Ser
50

FIG. 12

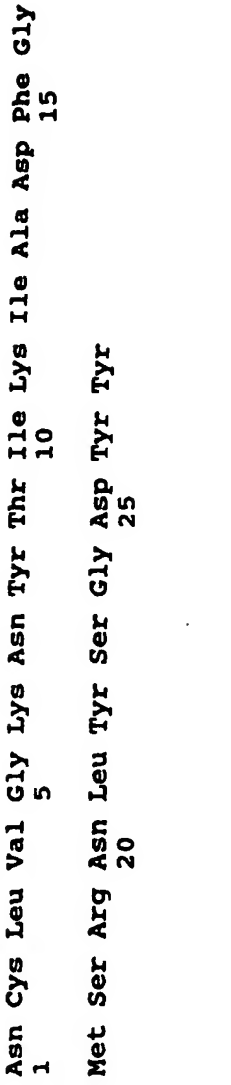
Asn Cys Leu Val Gly Lys Asn Tyr Thr Ile Lys Ile Ala Asp Phe Gly
1 5 10 15
Met Ser Arg Asn Leu Tyr Ser Gly Asp Tyr Tyr
20 25

FIG. 13

```
Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile Gly Asp
 1               5                  10                  15

Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr Lys Val
            20                  25                  30

Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro Glu Ser Leu
        35                  40                  45

Thr Glu Ser Leu Phe Ser Val Ala Ser Asp
    50                  55
```

FIG.14

```
Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp
 1               5                  10                  15

Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr
            20                  25                  30

Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile
        35                  40                  45

Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp
    50                  55
```

FIG. 15A

```
  1 TCGGGTCGGA CCCACGCGCA GCGGCCGGAG ATGCAGCGGG GCGCCGCGCT GTGCCTGCGA
    AGCCCAGCCT GGGTGCGCGT CGCCGGCCTC TACGTCGCCC CGCGGCGCGA CACGGACGCT
  1                                 M  Q  R  G   A  A  L   C  L  R

 61 CTGTGGCTCT GCCTGGGACT CCTGGACGGC CTGGTGAGTG GCTACTCCAT GACCCCCCCG
    GACACCGAGA CGGACCCTGA GGACCTGCCG GACCACTCAC CGATGAGGTA CTGGGGGGGC
 11 L  W  L  C   L  G  L   L  D  G   L  V  S  G   Y  S  M   T  P  P

121 ACCTTGAACA TCACGGAGGA GTCACACGTC ATCGACACCG GTGACAGCCT GTCCATCTCC
    TGGAACTTGT AGTGCCTCCT CAGTGTGCAG TAGCTGTGGC CACTGTCGGA CAGGTAGAGG
 31 T  L  N  I   T  E  E   S  H  V   I  D  T  G   D  S  L   S  I  S

181 TGCAGGGGAC AGCACCCCCT CGAGTGGGCT TGGCCAGGAG CTCAGGAGGC GCCAGCCACC
    ACGTCCCCTG TCGTGGGGGA GCTCACCCGA ACCGGTCCTC GAGTCCTCCG CGGTCGGTGG
 51 C  R  G  Q   H  P  L   E  W  A   W  P  G  A   Q  E  A   P  A  T

241 GGAGACAAGG ACAGCGAGGA CACGGGGGTG GTGCGAGACT GCGAGGGCAC AGACGCCAGG
    CCTCTGTTCC TGTCGCTCCT GTGCCCCCAC CACGCTCTGA CGCTCCCGTG TCTGCGGTCC
 71 G  D  K  D   S  E  D   T  G  V   V  R  D  C   E  G  T   D  A  R

301 CCCTACTGCA AGGTGTTGCT GCTGCACGAG GTACATGCCA ACGACACAGG CAGCTACGTC
    GGGATGACGT TCCACAACGA CGACGTGCTC CATGTACGGT TGCTGTGTCC GTCGATGCAG
 91 P  Y  C  K   V  L  L   L  H  E   V  H  A  N   D  T  G   S  Y  V

361 TGCTACTACA AGTACATCAA GGCACGCATC GAGGGCACCA CGGCCGCCAG CTCCTACGTG
    ACGATGATGT TCATGTAGTT CCGTGCGTAG CTCCCGTGGT GCCGGCGGTC GAGGATGCAC
111 C  Y  Y  K   Y  I  K   A  R  I   E  G  T  T   A  A  S   S  Y  V

421 TTCGTGAGAG ACTTTGAGCA GCCATTCATC AACAAGCCTG ACACGCTCTT GGTCAACAGG
    AAGCACTCTC TGAAACTCGT CGGTAAGTAG TTGTTCGGAC TGTGCGAGAA CCAGTTGTCC
131 F  V  R  D   F  E  Q   P  F  I   N  K  P  D   T  L  L   V  N  R

481 AAGGACGCCA TGTGGGTGCC CTGTCTGGTG TCCATCCCCG GCCTCAATGT CACGCTGCGC
    TTCCTGCGGT ACACCCACGG GACAGACCAC AGGTAGGGGC CGGAGTTACA GTGCGACGCG
151 K  D  A  M   W  V  P   C  L  V   S  I  P  G   L  N  V   T  L  R

541 TCGCAAAGCT CGGTGCTGTG GCCAGACGGG CAGGAGGTGG TGTGGGATGA CCGGCGGGGC
    AGCGTTTCGA GCCACGACAC CGGTCTGCCC GTCCTCCACC ACACCCTACT GGCCGCCCCG
171 S  Q  S  S   V  L  W   P  D  G   Q  E  V  V   W  D  D   R  R  G

601 ATGCTCGTGT CCACGCCACT GCTGCACGAT GCCCTGTACC TGCAGTGCGA GACCACCTGG
    TACGAGCACA GGTGCGGTGA CGACGTGCTA CGGGACATGG ACGTCACGCT CTGGTGGACC
191 M  L  V  S   T  P  L   L  H  D   A  L  Y  L   Q  C  E   T  T  W

661 GGAGACCAGG ACTTCCTTTC CAACCCCTTC CTGGTGCACA TCACAGGCAA CGAGCTCTAT
    CCTCTGGTCC TGAAGGAAAG GTTGGGGAAG GACCACGTGT AGTGTCCGTT GCTCGAGATA
211 G  D  Q  D   F  L  S   N  P  F   L  V  H  I   T  G  N   E  L  Y
```

FIG. 15B

```
 721 GACATCCAGC TGTTGCCCAG GAAGTCGCTG GAGCTGCTGG TAGGGGAGAA GCTGGTCCTG
     CTGTAGGTCG ACAACGGGTC CTTCAGCGAC CTCGACGACC ATCCCCTCTT CGACCAGGAC
 231 D  I  Q  L    L  P  R    K  S  L    E  L  L  V    G  E  K    L  V  L

 781 AACTGCACCG TGTGGGCTGA GTTTAACTCA GGTGTCACCT TTGACTGGGA CTACCCAGGG
     TTGACGTGGC ACACCCGACT CAAATTGAGT CCACAGTGGA AACTGACCCT GATGGGTCCC
 251 N  C  T  V    W  A  E    F  N  S    G  V  T  F    D  W  D    Y  P  G

 841 AAGCAGGCAG AGCGGGGTAA GTGGGTGCCC GAGCGACGCT CCCAGCAGAC CCACACAGAA
     TTCGTCCGTC TCGCCCCATT CACCCACGGG CTCGCTGCGA GGGTCGTCTG GGTGTGTCTT
 271 K  Q  A  E    R  G  K    W  V  P    E  R  R  S    Q  Q  T    H  T  E

 901 CTCTCCAGCA TCCTGACCAT CCACAACGTC AGCCAGCACG ACCTGGGCTC GTATGTGTGC
     GAGAGGTCGT AGGACTGGTA GGTGTTGCAG TCGGTCGTGC TGGACCCGAG CATACACACG
 291 L  S  S  I    L  T  I    H  N  V    S  Q  H  D    L  G  S    Y  V  C

 961 AAGGCCAACA ACGGCATCCA GCGATTTCGG GAGAGCACCG AGGTCATTGT GCATGAAAAT
     TTCCGGTTGT TGCCGTAGGT CGCTAAAGCC CTCTCGTGGC TCCAGTAACA CGTACTTTTA
 311 K  A  N  N    G  I  Q    R  F  R    E  S  T  E    V  I  V    H  E  N

1021 CCCTTCATCA GCGTCGAGTG GCTCAAAGGA CCCATCCTGG AGGCCACGGC AGGAGACGAG
     GGGAAGTAGT CGCAGCTCAC CGAGTTTCCT GGGTAGGACC TCCGGTGCCG TCCTCTGCTC
 331 P  F  I  S    V  E  W    L  K  G    P  I  L  E    A  T  A    G  D  E

1081 CTGGTGAAGC TGCCCGTGAA GCTGGCAGCG TACCCCCCGC CCGAGTTCCA GTGGTACAAG
     GACCACTTCG ACGGGCACTT CGACCGTCGC ATGGGGGGCG GGCTCAAGGT CACCATGTTC
 351 L  V  K  L    P  V  K    L  A  A    Y  P  P  P    E  F  Q    W  Y  K

1141 GATGGAAAGG CACTGTCCGG GCGCCACAGT CCACATGCCC TGGTGCTCAA GGAGGTGACA
     CTACCTTTCC GTGACAGGCC CGCGGTGTCA GGTGTACGGG ACCACGAGTT CCTCCACTGT
 371 D  G  K  A    L  S  G    R  H  S    P  H  A  L    V  L  K    E  V  T

1201 GAGGCCAGCA CAGGCACCTA CACCCTCGCC CTGTGGAACT CCGCTGCTGG CCTGAGGCGC
     CTCCGGTCGT GTCCGTGGAT GTGGGAGCGG GACACCTTGA GGCGACGACC GGACTCCGCG
 391 E  A  S  T    G  T  Y    T  L  A    L  W  N  S    A  A  G    L  R  R

1261 AACATCAGCC TGGAGCTGGT GGTGAATGTG CCCCCCCAGA TACATGAGAA GGAGGCCTCC
     TTGTAGTCGG ACCTCGACCA CCACTTACAC GGGGGGGTCT ATGTACTCTT CCTCCGGAGG
 411 N  I  S  L    E  L  V    V  N  V    P  P  Q  I    H  E  K    E  A  S

1321 TCCCCCAGCA TCTACTCGCG TCACAGCCGC CAGGCCCTCA CCTGCACGGC CTACGGGGTG
     AGGGGGTCGT AGATGAGCGC AGTGTCGGCG GTCCGGGAGT GGACGTGCCG GATGCCCCAC
 431 S  P  S  I    Y  S  R    H  S  R    Q  A  L  T    C  T  A    Y  G  V

1381 CCCCTGCCTC TCAGCATCCA GTGGCACTGG CGGCCCTGGA CACCCTGCAA GATGTTTGCC
     GGGGACGGAG AGTCGTAGGT CACCGTGACC GCCGGGACCT GTGGGACGTT CTACAAACGG
 451 P  L  P  L    S  I  Q    W  H  W    R  P  W  T    P  C  K    M  F  A

1441 CAGCGTAGTC TCCGGCGGCG GCAGCAGCAA GACCTCATGC CACAGTGCCG TGACTGGAGG
     GTCGCATCAG AGGCCGCCGC CGTCGTCGTT CTGGAGTACG GTGTCACGGC ACTGACCTCC
 471 Q  R  S  L    R  R  R    Q  Q  Q    D  L  M  P    Q  C  R    D  W  R
```

FIG. 15C

```
1501 GCGGTGACCA CGCAGGATGC CGTGAACCCC ATCGAGAGCC TGGACACCTG GACCGAGTTT
     CGCCACTGGT GCGTCCTACG GCACTTGGGG TAGCTCTCGG ACCTGTGGAC CTGGCTCAAA
 491 A  V  T  T   Q  D  A   V  N  P   I  E  S  L   D  T  W   T  E  F

1561 GTGGAGGGAA AGAATAAGAC TGTGAGCAAG CTGGTGATCC AGAATGCCAA CGTGTCTGCC
     CACCTCCCTT TCTTATTCTG ACACTCGTTC GACCACTAGG TCTTACGGTT GCACAGACGG
 511 V  E  G  K   N  K  T   V  S  K   L  V  I  Q   N  A  N   V  S  A

1621 ATGTACAAGT GTGTGGTCTC CAACAAGGTG GGCCAGGATG AGCGGCTCAT CTACTTCTAT
     TACATGTTCA CACACCAGAG GTTGTTCCAC CCGGTCCTAC TCGCCGAGTA GATGAAGATA
 531 M  Y  K  C   V  V  S   N  K  V   G  Q  D  E   R  L  I   Y  F  Y

1681 GTGACCACCA TCCCCGACGG CTTCACCATC GAATCCAAGC CATCCGAGGA GCTACTAGAG
     CACTGGTGGT AGGGGCTGCC GAAGTGGTAG CTTAGGTTCG GTAGGCTCCT CGATGATCTC
 551 V  T  T  I   P  D  G   F  T  I   E  S  K  P   S  E  E   L  L  E

1741 GGCCAGCCGG TGCTCCTGAG CTGCCAAGCC GACAGCTACA AGTACGAGCA TCTGCGCTGG
     CCGGTCGGCC ACGAGGACTC GACGGTTCGG CTGTCGATGT TCATGCTCGT AGACGCGACC
 571 G  Q  P  V   L  L  S   C  Q  A   D  S  Y  K   Y  E  H   L  R  W

1801 TACCGCCTCA ACCTGTCCAC GCTGCACGAT GCGCACGGGA ACCCGCTTCT GCTCGACTGC
     ATGGCGGAGT TGGACAGGTG CGACGTGCTA CGCGTGCCCT TGGGCGAAGA CGAGCTGACG
 591 Y  R  L  N   L  S  T   L  H  D   A  H  G  N   P  L  L   L  D  C

1861 AAGAACGTGC ATCTGTTCGC CACCCCTCTG GCCGCCAGCC TGGAGGAGGT GGCACCTGGG
     TTCTTGCACG TAGACAAGCG GTGGGGAGAC CGGCGGTCGG ACCTCCTCCA CCGTGGACCC
 611 K  N  V  H   L  F  A   T  P  L   A  A  S  L   E  E  V   A  P  G

1921 GCGCGCCACG CCACGCTCAG CCTGAGTATC CCCCGCGTCG CGCCCGAGCA CGAGGGCCAC
     CGCGCGGTGC GGTGCGAGTC GGACTCATAG GGGGCGCAGC GCGGGCTCGT GCTCCCGGTG
 631 A  R  H  A   T  L  S   L  S  I   P  R  V  A   P  E  H   E  G  H

1981 TATGTGTGCG AAGTGCAAGA CCGGCGCAGC CATGACAAGC ACTGCCACAA GAAGTACCTG
     ATACACACGC TTCACGTTCT GGCCGCGTCG GTACTGTTCG TGACGGTGTT CTTCATGGAC
 651 Y  V  C  E   V  Q  D   R  R  S   H  D  K  H   C  H  K   K  Y  L

2041 TCGGTGCAGG CCCTGGAAGC CCCTCGGCTC ACGCAGAACT TGACCGACCT CCTGGTGAAC
     AGCCACGTCC GGGACCTTCG GGGAGCCGAG TGCGTCTTGA ACTGGCTGGA GGACCACTTG
 671 S  V  Q  A   L  E  A   P  R  L   T  Q  N  L   T  D  L   L  V  N

2101 GTGAGCGACT CGCTGGAGAT GCAGTGCTTG GTGGCCGGAG CGCACGCGCC CAGCATCGTG
     CACTCGCTGA GCGACCTCTA CGTCACGAAC CACCGGCCTC GCGTGCGCGG GTCGTAGCAC
 691 V  S  D  S   L  E  M   Q  C  L   V  A  G  A   H  A  P   S  I  V

2161 TGGTACAAAG ACGAGAGGCT GCTGGAGGAA AAGTCTGGAG TCGACTTGGC GGACTCCAAC
     ACCATGTTTC TGCTCTCCGA CGACCTCCTT TTCAGACCTC AGCTGAACCG CCTGAGGTTG
 711 W  Y  K  D   E  R  L   L  E  E   K  S  G  V   D  L  A   D  S  N

2221 CAGAAGCTGA GCATCCAGCG CGTGCGCGAG GAGGATGCGG GACGCTATCT GTGCAGCGTG
     GTCTTCGACT CGTAGGTCGC GCACGCGCTC CTCCTACGCC CTGCGATAGA CACGTCGCAC
 731 Q  K  L  S   I  Q  R   V  R  E   E  D  A  G   R  Y  L   C  S  V
```

FIG. 15D

```
2281 TGCAACGCCA AGGGCTGCGT CAACTCCTCC GCCAGCGTGG CCGTGGAAGG CTCCGAGGAT
     ACGTTGCGGT TCCCGACGCA GTTGAGGAGG CGGTCGCACC GGCACCTTCC GAGGCTCCTA
 751 C  N  A  K   G  C  V   N  S  S   A  S  V  A   V  E  G   S  E  D

2341 AAGGGCAGCA TGGAGATCGT GATCCTTGTC GGTACCGGCG TCATCGCTGT CTTCTTCTGG
     TTCCCGTCGT ACCTCTAGCA CTAGGAACAG CCATGGCCGC AGTAGCGACA GAAGAAGACC
 771 K  G  S  M   E  I  V   I  L  V   G  T  G  V   I  A  V   F  F  W

2401 GTCCTCCTCC TCCTCATCTT CTGTAACATG AGGAGGCCGG CCCACGCAGA CATCAAGACG
     CAGGAGGAGG AGGAGTAGAA GACATTGTAC TCCTCCGGCC GGGTGCGTCT GTAGTTCTGC
 791 V  L  L  L   L  I  F   C  N  M   R  R  P  A   H  A  D   I  K  T

2461 GGCTACCTGT CCATCATCAT GGACCCCGGG GAGGTGCCTC TGGAGGAGCA ATGCGAATAC
     CCGATGGACA GGTAGTAGTA CCTGGGGCCC CTCCACGGAG ACCTCCTCGT TACGCTTATG
 811 G  Y  L  S   I  I  M   D  P  G   E  V  P  L   E  E  Q   C  E  Y

2521 CTGTCCTACG ATGCCAGCCA GTGGGAATTC CCCCGAGAGC GGCTGCACCT GGGGAGAGTG
     GACAGGATGC TACGGTCGGT CACCCTTAAG GGGGCTCTCG CCGACGTGGA CCCCTCTCAC
 831 L  S  Y  D   A  S  Q   W  E  F   P  R  E  R   L  H  L   G  R  V

2581 CTCGGCTACG GCGCCTTCGG GAAGGTGGTG GAAGCCTCCG CTTTCGGCAT CCACAAGGGC
     GAGCCGATGC CGCGGAAGCC CTTCCACCAC CTTCGGAGGC GAAAGCCGTA GGTGTTCCCG
 851 L  G  Y  G   A  F  G   K  V  V   E  A  S  A   F  G  I   H  K  G

2641 AGCAGCTGTG ACACCGTGGC CGTGAAAATG CTGAAAGAGG GCGCCACGGC CAGCGAGCAC
     TCGTCGACAC TGTGGCACCG GCACTTTTAC GACTTTCTCC CGCGGTGCCG GTCGCTCGTG
 871 S  S  C  D   T  V  A   V  K  M   L  K  E  G   A  T  A   S  E  H

2701 CGCGCGCTGA TGTCGGAGCT CAAGATCCTC ATTCACATCG GCAACCACCT CAACGTGGTC
     GCGCGCGACT ACAGCCTCGA GTTCTAGGAG TAAGTGTAGC CGTTGGTGGA GTTGCACCAG
 891 R  A  L  M   S  E  L   K  I  L   I  H  I  G   N  H  L   N  V  V

2761 AACCTCCTCG GGGCGTGCAC CAAGCCGCAG GGCCCCCTCA TGGTGATCGT GGAGTTCTGC
     TTGGAGGAGC CCCGCACGTG GTTCGGCGTC CCGGGGGAGT ACCACTAGCA CCTCAAGACG
 911 N  L  L  G   A  C  T   K  P  Q   G  P  L  M   V  I  V   E  F  C

2821 AAGTACGGCA ACCTCTCCAA CTTCCTGCGC GCCAAGCGGG ACGCCTTCAG CCCCTGCGCG
     TTCATGCCGT TGGAGAGGTT GAAGGACGCG CGGTTCGCCC TGCGGAAGTC GGGGACGCGC
 931 K  Y  G  N   L  S  N   F  L  R   A  K  R  D   A  F  S   P  C  A

2881 GAGAAGTCTC CCGAGCAGCG CGGACGCTTC CGCGCCATGG TGGAGCTCGC CAGGCTGGAT
     CTCTTCAGAG GGCTCGTCGC GCCTGCGAAG GCGCGGTACC ACCTCGAGCG GTCCGACCTA
 951 E  K  S  P   E  Q  R   G  R  F   R  A  M  V   E  L  A   R  L  D

2941 CGGAGGCGGC CGGGGAGCAG CGACAGGGTC CTCTTCGCGC GGTTCTCGAA GACCGAGGGC
     GCCTCCGCCG GCCCCTCGTC GCTGTCCCAG GAGAAGCGCG CCAAGAGCTT CTGGCTCCCG
 971 R  R  R  P   G  S  S   D  R  V   L  F  A  R   F  S  K   T  E  G

3001 GGAGCGAGGC GGGCTTCTCC AGACCAAGAA GCTGAGGACC TGTGGCTGAG CCCGCTGACC
     CCTCGCTCCG CCCGAAGAGG TCTGGTTCTT CGACTCCTGG ACACCGACTC GGGCGACTGG
 991 G  A  R  R   A  S  P   D  Q  E   A  E  D  L   W  L  S   P  L  T
```

FIG. 15E

```
3061 ATGGAAGATC TTGTCTGCTA CAGCTTCCAG GTGGCCAGAG GGATGGAGTT CCTGGCTTCC
     TACCTTCTAG AACAGACGAT GTCGAAGGTC CACCGGTCTC CCTACCTCAA GGACCGAAGG
1011 M  E  D  L   V  C  Y   S  F  Q   V  A  R  G   M  E  F   L  A  S

3121 CGAAAGTGCA TCCACAGAGA CCTGGCTGCT CGGAACATTC TGCTGTCGGA AAGCGACGTG
     GCTTTCACGT AGGTGTCTCT GGACCGACGA GCCTTGTAAG ACGACAGCCT TTCGCTGCAC
1031 R  K  C  I   H  R  D   L  A  A   R  N  I  L   L  S  E   S  D  V

3181 GTGAAGATCT GTGACTTTGG CCTTGCCCGG GACATCTACA AAGACCCTGA CTACGTCCGC
     CACTTCTAGA CACTGAAACC GGAACGGGCC CTGTAGATGT TTCTGGGACT GATGCAGGCG
1051 V  K  I  C   D  F  G   L  A  R   D  I  Y  K   D  P  D   Y  V  R

3241 AAGGGCAGTG CCCGGCTGCC CCTGAAGTGG ATGGCCCCTG AAAGCATCTT CGACAAGGTG
     TTCCCGTCAC GGGCCGACGG GGACTTCACC TACCGGGGAC TTTCGTAGAA GCTGTTCCAC
1071 K  G  S  A   R  L  P   L  K  W   M  A  P  E   S  I  F   D  K  V

3301 TACACCACGC AGAGTGACGT GTGGTCCTTT GGGGTGCTTC TCTGGGAGAT CTTCTCTCTG
     ATGTGGTGCG TCTCACTGCA CACCAGGAAA CCCCACGAAG AGACCCTCTA GAAGAGAGAC
1091 Y  T  T  Q   S  D  V   W  S  F   G  V  L  L   W  E  I   F  S  L

3361 GGGGCCTCCC CGTACCCTGG GGTGCAGATC AATGAGGAGT TCTGCCAGCG GCTGAGAGAC
     CCCCGGAGGG GCATGGGACC CCACGTCTAG TTACTCCTCA AGACGGTCGC CGACTCTCTG
1111 G  A  S  P   Y  P  G   V  Q  I   N  E  E  F   C  Q  R   L  R  D

3421 GGCACAAGGA TGAGGGCCCC GGAGCTGGCC ACTCCCGCCA TACGCCGCAT CATGCTGAAC
     CCGTGTTCCT ACTCCCGGGG CCTCGACCGG TGAGGGCGGT ATGCGGCGTA GTACGACTTG
1131 G  T  R  M   R  A  P   E  L  A   T  P  A  I   R  R  I   M  L  N

3481 TGCTGGTCCG GAGACCCCAA GGCGAGACCT GCATTCTCGG AGCTGGTGGA GATCCTGGGG
     ACGACCAGGC CTCTGGGGTT CCGCTCTGGA CGTAAGAGCC TCGACCACCT CTAGGACCCC
1151 C  W  S  G   D  P  K   A  R  P   A  F  S  E   L  V  E   I  L  G

3541 GACCTGCTCC AGGGCAGGGG CCTGCAAGAG GAAGAGGAGG TCTGCATGGC CCCGCGCAGC
     CTGGACGAGG TCCCGTCCCC GGACGTTCTC CTTCTCCTCC AGACGTACCG GGGCGCGTCG
1171 D  L  L  Q   G  R  G   L  Q  E   E  E  E  V   C  M  A   P  R  S

3601 TCTCAGAGCT CAGAAGAGGG CAGCTTCTCG CAGGTGTCCA CCATGGCCCT ACACATCGCC
     AGAGTCTCGA GTCTTCTCCC GTCGAAGAGC GTCCACAGGT GGTACCGGGA TGTGTAGCGG
1191 S  Q  S  S   E  E  G   S  F  S   Q  V  S  T   M  A  L   H  I  A

3661 CAGGCTGACG CTGAGGACAG CCCGCCAAGC CTGCAGCGCC ACAGCCTGGC CGCCAGGTAT
     GTCCGACTGC GACTCCTGTC GGGCGGTTCG GACGTCGCGG TGTCGGACCG GCGGTCCATA
1211 Q  A  D  A   E  D  S   P  P  S   L  Q  R  H   S  L  A   A  R  Y

3721 TACAACTGGG TGTCCTTTCC CGGGTGCCTG GCCAGAGGGG CTGAGACCCG TGGTTCCTCC
     ATGTTGACCC ACAGGAAAGG GCCCACGGAC CGGTCTCCCC GACTCTGGGC ACCAAGGAGG
1231 Y  N  W  V   S  F  P   G  C  L   A  R  G  A   E  T  R   G  S  S

3781 AGGATGAAGA CATTTGAGGA ATTCCCCATG ACCCCAACGA CCTACAAAGG CTCTGTGGAC
     TCCTACTTCT GTAAACTCCT TAAGGGGTAC TGGGGTTGCT GGATGTTTCC GAGACACCTG
1251 R  M  K  T   F  E  E   F  P  M   T  P  T  T   Y  K  G   S  V  D
```

FIG. 15F

```
3841 AACCAGACAG ACAGTGGGAT GGTGCTGGCC TCGGAGGAGT TTGAGCAGAT AGAGAGCAGG
     TTGGTCTGTC TGTCACCCTA CCACGACCGG AGCCTCCTCA AACTCGTCTA TCTCTCGTCC
1271 N  Q  T  D   S  G  M   V  L  A   S  E  E  F   E  Q  I   E  S  R

3901 CATAGACAAG AAAGCGGCTT CAGGTAGCTG AAGCAGAGAG AGAGAAGGCA GCATACGTCA
     GTATCTGTTC TTTCGCCGAA GTCCATCGAC TTCGTCTCTC TCTCTTCCGT CGTATGCAGT
1291 H  R  Q  E   S  G  F   R  O

3961 GCATTTTCTT CTCTGCACTT ATAAGAAAGA TCAAAGACTT TAAGACTTTC GCTATTTCTT
     CGTAAAAGAA GAGACGTGAA TATTCTTTCT AGTTTCTGAA ATTCTGAAAG CGATAAAGAA

4021 CTGCTATCTA CTACAAACTT CAAAGAGGAA CCAGGAGGCC AAGAGGAGCA TGAAAGTGGA
     GACGATAGAT GATGTTTGAA GTTTCTCCTT GGTCCTCCGG TTCTCCTCGT ACTTTCACCT

4081 CAAGGAGTGT GACCACTGAA GCACCACAGG GAGGGGTTAG GCCTCCGGAT GACTGCGGGC
     GTTCCTCACA CTGGTGACTT CGTGGTGTCC CTCCCCAATC CGGAGGCCTA CTGACGCCCG

4141 AGGCCTGGAT AATATCCAGC CTCCCACAAG AAGCTGGTGG AGCAGAGTGT TCCCTGACTC
     TCCGGACCTA TTATAGGTCG GAGGGTGTTC TTCGACCACC TCGTCTCACA AGGGACTGAG

4201 CTCCAAGGAA AGGGAGACGC CCTTTCATGG TCTGCTGAGT AACAGGTGCC TTCCCAGACA
     GAGGTTCCTT TCCCTCTGCG GGAAAGTACC AGACGACTCA TTGTCCACGG AAGGGTCTGT

4261 CTGGCGTTAC TGCTTGACCA AAGAGCCCTC AAGCGGCCCT TATGCCAGCG TGACAGAGGG
     GACCGCAATG ACGAACTGGT TTCTCGGGAG TTCGCCGGGA ATACGGTCGC ACTGTCTCCC

4321 CTCACCTCTT GCCTTCTAGG TCACTTCTCA CAATGTCCCT TCAGCACCTG ACCCTGTGCC
     GAGTGGAGAA CGGAAGATCC AGTGAAGAGT GTTACAGGGA AGTCGTGGAC TGGGACACGG

4381 CGCCAGTTAT TCCTTGGTAA TATGAGTAAT ACATCAAAGA GTAGT
     GCGGTCAATA AGGAACCATT ATACTCATTA TGTAGTTTCT CATCA
```

FIG. 16A

```
  1 ATGGCTGGGA TTTTCTATTT CGCCCTATTT TCGTGTCTCT TCGGGATTTG
    TACCGACCCT AAAAGATAAA GCGGGATAAA AGCACAGAGA AGCCCTAAAC
  1 MetAlaGlyI lePheTyrPh eAlaLeuPhe SerCysLeuP heGlyIleCy
    CGACGCTGTC ACAGGTTCCA GGGTATACCC CGCGAATGAA GTTACCTTAT
    GCTGCGACAG TGTCCAAGGT CCCATATGGG GCGCTTACTT CAATGGAATA
    sAspAlaVal ThrGlySerA rgValTyrPr oAlaAsnGlu ValThrLeuLeu

101 TGGATTCCAG ATCTGTTCAG GGAGAACTTG GGTGGATAGC AAGCCCTCTG
    ACCTAAGGTC TAGACAAGTC CCTCTTGAAC CCACCTATCG TTCGGGAGAC
 35   AspSerAr gSerValGln GlyGluLeuG lyTrpIleAl aSerProLeu
    GAAGGAGGGT GGGAGGAAGT GAGTATCATG GATGAAAAAA ATACACCAAT
    CTTCCTCCCA CCCTCCTTCA CTCATAGTAC CTACTTTTTT TATGTGGTTA
    GluGlyGlyT rpGluGluVa lSerIleMet AspGluLysA snThrProIle

201 CCGAACCTAC CAAGTGTGCA ATGTGATGGA ACCCAGCCAG AATAACTGGC
    GGCTTGGATG GTTCACACGT TACACTACCT TGGGTCGGTC TTATTGACCG
 68  ArgThrTyr GlnValCysA snValMetGl uProSerGln AsnAsnTrpL
    TACGAACTGA TTGGATCACC CGAGAAGGGG CTCAGAGGGT GTATATTGAG
    ATGCTTGACT AACCTAGTGG GCTCTTCCCC GAGTCTCCCA CATATAACTC
    euArgThrAs pTrpIleThr ArgGluGlyA laGlnArgVa lTyrIleGlu

301 ATTAAATTCA CCTTGAGGGA CTGCAATAGT CTTCCGGGCG TCATGGGGAC
    TAATTTAAGT GGAACTCCCT GACGTTATCA GAAGGCCCGC AGTACCCCTG
101 IleLysPheT hrLeuArgAs pCysAsnSer LeuProGlyV alMetGlyTh
    TTGCAAGGAG ACGTTTAACC TGTACTACTA TGAATCAGAC AACGACAAAG
    AACGTTCCTC TGCAAATTGG ACATGATGAT ACTTAGTCTG TTGCTGTTTC
    rCysLysGlu ThrPheAsnL euTyrTyrTy rGluSerAsp AsnAspLysGlu
```

FIG. 16B

```
401 AGCGTTTCAT CAGAGAGAAC CAGTTTGTCA AAATTGACAC CATTGCTGCT
    TCGCAAAGTA GTCTCTCTTG GTCAAACAGT TTTAACTGTG GTAACGACGA
135   ArgPheIl eArgGluAsn GlnPheValL ysIleAspTh rIleAlaAla
    GATGAGAGCT TCACCCAAGT GGACATTGGT GACAGAATCA TGAAGCTGAA
    CTACTCTCGA AGTGGGTTCA CCTGTAACCA CTGTCTTAGT ACTTCGACTT
    AspGluSerP heThrGlnVa lAspIleGly AspArgIleM etLysLeuAsn
501 CACCGAGATC CGGGATGTAG GGCCATTAAG CAAAAAGGGG TTTTACCTGG
    GTGGCTCTAG GCCCTACATC CCGGTAATTC GTTTTTCCCC AAAATGGACC
168  ThrGluIle ArgAspValG lyProLeuSe rLysLysGly PheTyrLeuA
    CTTTTCAGGA TGTGGGGGCC TGCATCGCCC TGGTATCAGT CCGTGTGTTC
    GAAAAGTCCT ACACCCCCGG ACGTAGCGGG ACCATAGTCA GGCACACAAG
    laPheGlnAs pValGlyAla CysIleAlaL euValSerVa lArgValPhe
601 TATAAAAAGT GTCCACTCAC AGTCCGCAAT CTGGCCCAGT TTCCTGACAC
    ATATTTTTCA CAGGTGAGTG TCAGGCGTTA GACCGGGTCA AAGGACTGTG
201 TyrLysLysC ysProLeuTh rValArgAsn LeuAlaGlnP heProAspTh
    CATCACAGGG GCTGATACGT CTTCCCTGGT GGAAGTTCGA GGCTCCTGTG
    GTAGTGTCCC CGACTATGCA GAAGGGACCA CCTTCAAGCT CCGAGGACAC
    rIleThrGly AlaAspThrS erSerLeuVa lGluValArg GlySerCysVal
701 TCAACAACTC AGAAGAGAAA GATGTGCCAA AAATGTACTG TGGGGCAGAT
    AGTTGTTGAG TCTTCTCTTT CTACACGGTT TTTACATGAC ACCCCGTCTA
235   AsnAsnSe rGluGluLys AspValProL ysMetTyrCy sGlyAlaAsp
    GGTGAATGGC TGGTACCCAT TGGCAACTGC CTATGCAACG CTGGGCATGA
    CCACTTACCG ACCATGGGTA ACCGTTGACG GATACGTTGC GACCCGTACT
    GlyGluTrpL euValProIl eGlyAsnCys LeuCysAsnA laGlyHisGlu
801 GGAGCGGAGC GGAGAATGCC AAGCTTGCAA AATTGGATAT TACAAGGCTC
    CCTCGCCTCG CCTCTTACGG TTCGAACGTT TTAACCTATA ATGTTCCGAG
268  GluArgSer GlyGluCysG lnAlaCysLy sIleGlyTyr TyrLysAlaL
    TCTCCACGGA TGCCACCTGT GCCAAGTGCC CACCCCACAG CTACTCTGTC
    AGAGGTGCCT ACGGTGGACA CGGTTCACGG GTGGGGTGTC GATGAGACAG
    euSerThrAs pAlaThrCys AlaLysCysP roProHisSe rTyrSerVal
```

FIG. 16C

```
 901 TGGGAAGGAG CCACCTCGTG CACCTGTGAC CGAGGCTTTT TCAGAGCTGA
     ACCCTTCCTC GGTGGAGCAC GTGGACACTG GCTCCGAAAA AGTCTCGACT
 301 TrpGluGlyA laThrSerCy sThrCysAsp ArgGlyPheP heArgAlaAs
     CAACGATGCT GCCTCTATGC CCTGCACCCG TCCACCATCT GCTCCCCTGA
     GTTGCTACGA CGGAGATACG GGACGTGGGC AGGTGGTAGA CGAGGGGACT
     pAsnAspAla AlaSerMetP roCysThrAr gProProSer AlaProLeuAsn
1001 ACTTGATTTC AAATGTCAAC GAGACATCTG TGAACTTGGA ATGGAGTAGC
     TGAACTAAAG TTTACAGTTG CTCTGTAGAC ACTTGAACCT TACCTCATCG
 335   LeuIleSe rAsnValAsn GluThrSerV alAsnLeuGl uTrpSerSer
     CCTCAGAATA CAGGTGGCCG CCAGGACATT TCCTATAATG TGGTATGCAA
     GGAGTCTTAT GTCCACCGGC GGTCCTGTAA AGGATATTAC ACCATACGTT
     ProGlnAsnT hrGlyGlyAr gGlnAspIle SerTyrAsnV alValCysLys
1101 GAAATGTGGA GCTGGTGACC CCAGCAAGTG CCGACCCTGT GGAAGTGGGG
     CTTTACACCT CGACCACTGG GGTCGTTCAC GGCTGGGACA CCTTCACCCC
 368  LysCysGly AlaGlyAspP roSerLysCy sArgProCys GlySerGlyV
     TCCACTACAC CCCACAGCAG AATGGCTTGA AGACCACCAA AGGCTCCATC
     AGGTGATGTG GGGTGTCGTC TTACCGAACT TCTGGTGGTT TCCGAGGTAG
     alHisTyrTh rProGlnGln AsnGlyLeuL ysThrThrLy sGlySerIle
1201 ACTGACCTCC TAGCTCATAC CAATTACACC TTTGAAATCT GGGCTGTGAA
     TGACTGGAGG ATCGAGTATG GTTAATGTGG AAACTTTAGA CCCGACACTT
 401 ThrAspLeuL euAlaHisTh rAsnTyrThr PheGluIleT rpAlaValAs
     TGGAGTGTCC AAATATAACC CTAACCCAGA CCAATCAGTT TCTGTCACTG
     ACCTCACAGG TTTATATTGG GATTGGGTCT GGTTAGTCAA AGACAGTGAC
     nGlyValSer LysTyrAsnP roAsnProAs pGlnSerVal SerValThrVal
1301 TGACCACCAA CCAAGCAGCA CCATCATCCA TTGCTTTGGT CCAGGCTAAA
     ACTGGTGGTT GGTTCGTCGT GGTAGTAGGT AACGAAACCA GGTCCGATTT
 435   ThrThrAs nGlnAlaAla ProSerSerI leAlaLeuVa lGlnAlaLys
     GAAGTCACAA GATACAGTGT GGCACTGGCT TGGCTGGAAC CAGATCGGCC
     CTTCAGTGTT CTATGTCACA CCGTGACCGA ACCGACCTTG GTCTAGCCGG
     GluValThrA rgTyrSerVa lAlaLeuAla TrpLeuGluP roAspArgPro
```

FIG. 16D

```
1401 CAATGGGGTA ATCCTGGAAT ATGAAGTCAA GTATTATGAG AAGGATCAGA
     GTTACCCCAT TAGGACCTTA TACTTCAGTT CATAATACTC TTCCTAGTCT
 468  AsnGlyVal IleLeuGluT yrGluValLy sTyrTyrGlu LysAspGlnA
     ATGAGCGAAG CTATCGTATA GTTCGGACAG CTGCCAGGAA CACAGATATC
     TACTCGCTTC GATAGCATAT CAAGCCTGTC GACGGTCCTT GTGTCTATAG
     snGluArgSe rTyrArgIle ValArgThrA laAlaArgAs nThrAspIle
1501 AAAGGCCTGA ACCCTCTCAC TTCCTATGTT TTCCACGTGC GAGCCAGGAC
     TTTCCGGACT TGGGAGAGTG AAGGATACAA AAGGTGCACG CTCGGTCCTG
 501 LysGlyLeuA snProLeuTh rSerTyrVal PheHisValA rgAlaArgTh
     AGCAGCTGGC TATGGAGACT TCAGTGAGCC CTTGGAGGTT ACAACCAACA
     TCGTCGACCG ATACCTCTGA AGTCACTCGG GAACCTCCAA TGTTGGTTGT
     rAlaAlaGly TyrGlyAspP heSerGluPr oLeuGluVal ThrThrAsnThr
1601 CAGTGCCTTC CCGGATCATT GGAGATGGGG CTAACTCCAC AGTCCTTCTG
     GTCACGGAAG GGCCTAGTAA CCTCTACCCC GATTGAGGTG TCAGGAAGAC
 535   ValProSe rArgIleIle GlyAspGlyA laAsnSerTh rValLeuLeu
     GTCTCTGTCT CGGGCAGTGT GGTGCTGGTG GTAATTCTCA TTGCAGCTTT
     CAGAGACAGA GCCCGTCACA CCACGACCAC CATTAAGAGT AACGTCGAAA
     ValSerValS erGlySerVa lValLeuVal ValIleLeuI leAlaAlaPhe
1701 TGTCATCAGC CGGAGACGGA GTAAATACAG TAAAGCCAAA CAAGAAGCGG
     ACAGTAGTCG GCCTCTGCCT CATTTATGTC ATTTCGGTTT GTTCTTCGCC
 568  ValIleSer ArgArgArgS erLysTyrSe rLysAlaLys GlnGluAlaA
     ATGAAGAGAA ACATTTGAAT CAAGGTGTAA GAACATATGT GGACCCCTTT
     TACTTCTCTT TGTAAACTTA GTTCCACATT CTTGTATACA CCTGGGGAAA
     spGluGluLy sHisLeuAsn GlnGlyValA rgThrTyrVa lAspProPhe
```

FIG. 16E

```
1801 ACGTACGAAG ATCCCAACCA AGCAGTGCGA GAGTTTGCCA AAGAAATTGA
     TGCATGCTTC TAGGGTTGGT TCGTCACGCT CTCAAACGGT TTCTTTAACT
 601 ThrTyrGluA spProAsnGl nAlaValArg GluPheAlaL ysGluIleAs
     CGCATCCTGC ATTAAGATTG AAAAAGTTAT AGGAGTTGGT GAATTTGGTG
     GCGTAGGACG TAATTCTAAC TTTTTCAATA TCCTCAACCA CTTAAACCAC
     pAlaSerCys IleLysIleG luLysValIl eGlyValGly GluPheGlyGlu
1901 AGGTATGCAG TGGGCGTCTC AAAGTGCCTG GCAAGAGAGA GATCTGTGTG
     TCCATACGTC ACCCGCAGAG TTTCACGGAC CGTTCTCTCT CTAGACACAC
 635   ValCysSe rGlyArgLeu LysValProG lyLysArgGl uIleCysVal
     GCTATCAAGA CTCTGAAAGC TGGTTATACA GACAAACAGA GGAGAGACTT
     CGATAGTTCT GAGACTTTCG ACCAATATGT CTGTTTGTCT CCTCTCTGAA
     AlaIleLysT hrLeuLysAl aGlyTyrThr AspLysGlnA rgArgAspPhe
2001 CCTGAGTGAG GCCAGCATCA TGGGACAGTT TGACCATCCG AACATCATTC
     GGACTCACTC CGGTCGTAGT ACCCTGTCAA ACTGGTAGGC TTGTAGTAAG
 668  LeuSerGlu AlaSerIleM etGlyGlnPh eAspHisPro AsnIleIleH
     ACTTGGAAGG CGTGGTCACT AAATGTAAAC CAGTAATGAT CATAACAGAG
     TGAACCTTCC GCACCAGTGA TTTACATTTG GTCATTACTA GTATTGTCTC
     isLeuGluGl yValValThr LysCysLysP roValMetIl eIleThrGlu
2101 TACATGGAGA ATGGCTCCTT GGATGCATTC CTCAGGAAAA ATGATGGCAG
     ATGTACCTCT TACCGAGGAA CCTACGTAAG GAGTCCTTTT TACTACCGTC
 701 TyrMetGluA snGlySerLe uAspAlaPhe LeuArgLysA snAspGlyAr
     ATTTACAGTC ATTCAGCTGG TGGGCATGCT TCGTGGCATT GGGTCTGGGA
     TAAATGTCAG TAAGTCGACC ACCCGTACGA AGCACCGTAA CCCAGACCCT
     gPheThrVal IleGlnLeuV alGlyMetLe uArgGlyIle GlySerGlyMet
2201 TGAAGTATTT ATCTGATATG AGCTATGTGC ATCGTGATCT GGCCGCACGG
     ACTTCATAAA TAGACTATAC TCGATACACG TAGCACTAGA CCGGCGTGCC
 735   LysTyrLe uSerAspMet SerTyrValH isArgAspLe uAlaAlaArg
     AACATCCTGG TGAACAGCAA CTTGGTCTGC AAAGTGTCTG ATTTTGGCAT
     TTGTAGGACC ACTTGTCGTT GAACCAGACG TTTCACAGAC TAAAACCGTA
     AsnIleLeuV alAsnSerAs nLeuValCys LysValSerA spPheGlyMet
```

FIG. 16F

```
2301 GTCCCGAGTG CTTGAGGATG ATCCGGAAGC AGCTTACACC ACCAGGGGTG
     CAGGGCTCAC GAACTCCTAC TAGGCCTTCG TCGAATGTGG TGGTCCCCAC
 768  SerArgVal LeuGluAspA spProGluAl aAlaTyrThr ThrArgGlyG
     GCAAGATTCC TATCCGGTGG ACTGCGCCAG AAGCAATTGC CTATCGTAAA
     CGTTCTAAGG ATAGGCCACC TGACGCGGTC TTCGTTAACG GATAGCATTT
     lyLysIlePr oIleArgTrp ThrAlaProG luAlaIleAl aTyrArgLys
2401 TTCACATCAG CAAGTGATGT ATGGAGCTAT GGAATCGTTA TGTGGGAAGT
     AAGTGTAGTC GTTCACTACA TACCTCGATA CCTTAGCAAT ACACCCTTCA
 801 PheThrSerA laSerAspVa lTrpSerTyr GlyIleValM etTrpGluVa
     GATGTCGTAC GGGGAGAGGC CCTATTGGGA TATGTCCAAT CAAGATGTGA
     CTACAGCATG CCCCTCTCCG GGATAACCCT ATACAGGTTA GTTCTACACT
     lMetSerTyr GlyGluArgP roTyrTrpAs pMetSerAsn GlnAspValIle
2501 TTAAAGCCAT TGAGGAAGGC TATCGGTTAC CCCCTCCAAT GGACTGCCCC
     AATTTCGGTA ACTCCTTCCG ATAGCCAATG GGGGAGGTTA CCTGACGGGG
 835   LysAlaIl eGluGluGly TyrArgLeuP roProProMe tAspCysPro
     ATTGCGCTCC ACCAGCTGAT GCTAGACTGC TGGCAGAAGG AGAGGAGCGA
     TAACGCGAGG TGGTCGACTA CGATCTGACG ACCGTCTTCC TCTCCTCGCT
     IleAlaLeuH isGlnLeuMe tLeuAspCys TrpGlnLysG luArgSerAsp
2601 CAGGCCTAAA TTTGGGCAGA TTGTCAACAT GTTGGACAAA CTCATCCGCA
     GTCCGGATTT AAACCCGTCT AACAGTTGTA CAACCTGTTT GAGTAGGCGT
 868  ArgProLys PheGlyGlnI leValAsnMe tLeuAspLys LeuIleArgA
     ACCCCAACAG CTTGAAGAGG ACAGGGACGG AGAGCTCCAG ACCTAACACT
     TGGGGTTGTC GAACTTCTCC TGTCCCTGCC TCTCGAGGTC TGGATTGTGA
     snProAsnSe rLeuLysArg ThrGlyThrG luSerSerAr gProAsnThr
```

FIG. 16G

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2701 GCCTTGTTGG ATCCAAGCTC CCCTGAATTC TCTGCTGTGG TATCAGTGGG
     CGGAACAACC TAGGTTCGAG GGGACTTAAG AGACGACACC ATAGTCACCC
 901 AlaLeuLeuA spProSerSe rProGluPhe SerAlaValV alSerValGl
     CGATTGGCTC CAGGCCATTA AAATGGACCG GTATAAGGAT AACTTCACAG
     GCTAACCGAG GTCCGGTAAT TTTACCTGGC CATATTCCTA TTGAAGTGTC
     yAspTrpLeu GlnAlaIleL ysMetAspAr gTyrLysAsp AsnPheThrAla
2801 CTGCTGGTTA TACCACACTA GAGGCTGTGG TGCACGTGAA CCAGGAGGAC
     GACGACCAAT ATGGTGTGAT CTCCGACACC ACGTGCACTT GGTCCTCCTG
 935   AlaGlyTy rThrThrLeu GluAlaValV alHisValAs nGlnGluAsp
     CTGGCAAGAA TTGGTATCAC AGCCATCACA CACCAGAATA AGATTTTGAG
     GACCGTTCTT AACCATAGTG TCGGTAGTGT GTGGTCTTAT TCTAAAACTC
     LeuAlaArgI leGlyIleTh rAlaIleThr HisGlnAsnL ysIleLeuSer
2901 CAGTGTCCAG GCAATGCGAA CCCAAATGCA GCAGATGCAC GGCAGAATGG
     GTCACAGGTC CGTTACGCTT GGGTTTACGT CGTCTACGTG CCGTCTTACC
 968  SerValGln AlaMetArgT hrGlnMetGl nGlnMetHis GlyArgMetV
     TTCCCGTCTG AGCCAGTACT GAATAAACTC AAAACTCTTG AAATTAGTTT
     AAGGGCAGAC TCGGTCATGA CTTATTTGAG TTTTGAGAAC TTTAATCAAA
     alProValOp *AlaSerThr GluOc*ThrG lnAsnSerOp *AsnAm*Phe
3001 ACCTCATCCA TGCACTTTAA TTGAAGAACT GCACTTTTTT TACTTCGTCT
     TGGAGTAGGT ACGTGAAATT AACTTCTTGA CGTGAAAAAA ATGAAGCAGA
1001 ThrSerSerM etHisPheAs nOp*ArgThr AlaLeuPheL euLeuArgLe
     TCGCCCTCTG AAATTAAAGA AATGAAAAAA AAAAAACAAT ATCTGCAGCG
     AGCGGGAGAC TTTAATTTCT TTACTTTTTT TTTTTGTTA TAGACGTCGC
     uArgProLeu LysLeuLysL ysOp*LysLy sLysAsnAsn IleCysSerVal
```

FIG. 16H

```
3101 TTGCTTGGTG CACAGATTGC TGAAACTGTG GGGCTTACAG AAATGACTGC
     AACGAACCAC GTGTCTAACG ACTTTGACAC CCCGAATGTC TTTACTGACG
1035   AlaTrpCv sThrAspCvs Op*AsnCvsG lvAlaTvrAr gAsnAspCvs
     CGGTCATTTG AATGAGACCT GGAACAAATC GTTTCTCAGA AGTACTTTTC
     GCCAGTAAAC TTACTCTGGA CCTTGTTTAG CAAAGAGTCT TCATGAAAAG
     ArgSerPheG luOp*AspLe uGluGlnIle ValSerGlnL ysTyrPheSer
3201 TGTTCATCAC CAGTCTGTAA AATACATGTA CCTATAGAAA TAGAACACTG
     ACAAGTAGTG GTCAGACATT TTATGTACAT GGATATCTTT ATCTTGTGAC
1068  ValHisHis GlnSerValL ysTyrMetTy rLeuAm*Lys Am*AsnThrA
     CCTCTGAGTT TTGATGCTGT ATTTGCTGCC AGACACTGAG CTTCTGAGAC
     GGAGACTCAA AACTACGACA TAAACGACGG TCTGTGACTC GAAGACTCTG
     laSerGluPh eOp*CysCys IleCysCysG lnThrLeuSe rPheOp*Asp
3301 ATCCCTGATT CTCTCTCCAT TTGGAATTAC AACGGTCGAC GAGCTCGA
     TAGGGACTAA GAGAGAGGTA AACCTTAATG TTGCCAGCTG CTCGAGCT
1101 IleProAspS erLeuSerIl eTrpAsnTyr AsnGlyArgA rgAlaArg
```

INTERNATIONAL SEARCH REPORT

Intern: ul Application No
PCT/US 95/04228

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K16/28 C07K19/00 C12N5/10 C12N15/85
A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 15201 (NEW ENGLAND DEACONESS HOSPITAL) 5 August 1993 see page 13, line 1-13 see figures see claims ---	1-15
A	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 36, 25 December 1992 BALTIMORE, MD, USA, pages 26166-26171, M. MARK ET AL. 'Expression and characterization of hepatocyte growth factor receptor-IgG fusion proteins.' see the whole document --- -/--	8-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1995	01.08.95

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF CELLULAR PHYSIOLOGY, vol. 158, no. 3, March 1994 NEW YORK, NY, USA, pages 545-554, L. ASHMAN ET AL. 'Epitope mapping and functional studies with three monoclonal antibodies to the c-kit receptor tyrosine kinase, YB5.B8, 17F11, and SR-1.' see abstract ---	1-7
A	GROWTH REGULATION, vol. 1, no. 2, June 1991 EDINBURGH, GB, pages 72-82, J. SARUP ET AL. 'Characterization of an anti-p185HER2 monoclonal antibody that stimulates receptor function and inhibits tumor cell growth.' see abstract ---	1-7
A	CANCER RESEARCH, vol. 52, no. 3, 1 February 1992 PHILADELPHIA, PA, USA, pages 746-748, O. APRELIKOVA ET AL. 'FLT4, a novel class III receptor tyrosine kinase in chromosome 5q33-qter.' see abstract see figure 1 ---	8-15
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 92, no. 6, 14 March 1995 WASHINGTON, DC, USA, pages 1866-1870, B. BENNETT ET AL. 'Molecular cloning of a ligand for the EPH-related receptor protein-tyrosine kinase Htk.' see the whole document ---	1-15
P,X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 19, 13 May 1994 BALTIMORE, MD, USA, pages 14211-14218, B. BENNETT ET AL. 'Cloning and characterization of HTK, a novel transmembrane tyrosine kinase of the EPH subfamily.' see the whole document --- -/--	1,3,7-9, 11-15

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	BLOOD, vol. 84, no. 8, 15 October 1994 NEW YORK, NY, USA, pages 2422-2430, F. ZEIGLER ET AL. 'Cellular and molecular characterization of the role of the FLK-2/FLT-3 receptor tyrosine kinase in hematopoietic stem cells.' see the whole document	1-7

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern... al Application No
PCT/US 95/04228

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9315201	05-08-93	AU-B-	3482493	01-09-93
		CA-A-	2128722	05-08-93
		EP-A-	0624192	17-11-94
		JP-T-	7504813	01-06-95